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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

OCTOBER 1938

STUDIES ON THE CORTICAL REPRESENTATION OF SOMATIC SENSIBILITY

Harvey Lecture, February 17, 1938

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THE information at present available concerning the representation of somatic sensibility in the cerebral cortex is admittedly fragmentary. This state of affairs is doubtless due to the peculiar difficulties which attend all investigations of sensory functions. Extensive experiments can be carried out with proper control procedures in animals, but here the interpretation of results is often made difficult by the fact that it is not always easy, in the absence of a verbal report, to distinguish between a motor and a sensory deficit, and to consider sensation in an animal is to draw an inference which, however plausible, has no place in objective physiological work. While clinical studies in this field possess the great advantage that they permit an examination of sensory experience, they suffer from the fact that the nature of the material greatly limits the range of experimentation.

In the exploration of the somatic sensory functions of the cortex a number of methods have been used. Some idea of the areas concerned has been gained by inference from the distribution of thalamocortical

fibers mediating deep and cutaneous sensibility. After interruption of these at or near the thalamus, Poliak[1] traced their degeneration into the cortex. His results in the monkey indicate that the somesthetic projection area is a large one extending "about equally, orally and caudally, from the sulcus centralis as well as over the internal face of the hemisphere where it reaches the sulcus cinguli." By studying the retrograde degeneration in the thalamus following removal of one or another part of this area Clark and Boggon,[2] Walker[3] and others have added important details to our anatomical knowledge of this representation. The interpretation of these findings in terms of function is one of the pressing problems confronting neurophysiologists.

In the clinical studies of this subject the most definite results have been obtained by stimulating the exposed cortex of the human subject in the course of operative procedures not involving a general anesthetic. This method was early used by Cushing[4] to study sensation, and more recently others, notably Foerster[5] and Penfield,[6] have published detailed maps of the somesthetic representation indicated by it. The results obtained by different neurosurgeons have on the whole been in fair accord as regards the sequence of the representation of the parts of the body, but there is some disagreement about the question of bilateral representation and the matter of overlap of sensory and motor areas.[6] A valid criticism of this method is that application of a stimulating current to tissue of such histological complexity cannot be expected to give the same result as the arrival of definitely grouped corticipetal nerve impulses. This is doubtless reflected in the nature of the sensations experienced by the subjects. Most frequently numbness and tingling, only rarely definite sensations comparable to those experienced in normal life, are reported. In brief, the cortical stimulation experiments have yielded much important information regarding the locus of representation, but have told us little about the sensory modalities represented.

Many studies of the effects of cortical ablations and lesions upon sensory functions have been made. Much of the clinical work has suffered seriously from inability to determine the exact extent of the lesion. In the experiments on animals difficulties have arisen from the fact that usually the only available criterion of a sensory disturbance following an ablation is a failure of or a deficiency in some motor performance. Therefore, if the sensory modality under investigation is one which is represented in the cortical area governing the motor act, the ablation

method is useless. This point is emphasized in view of the evidence indicating that the region of the motor cortex subserves certain sensory functions.[6,7,8] When, however, it can be shown that the cortical sensory and motor mechanisms subserving an act are spatially separate the method may yield illuminating results.

Significant results bearing on the problem of the somatic sensory functions of the cortex have been obtained in animal experiments by the method of local strychninization. Dusser de Barenne[7] has shown that the local application of strychnine to certain parts of the cortex of cats and monkeys produces signs of marked hyperexcitability of the skin to tactile, thermal and nociceptive stimuli and of the deeper structures to pressure. In the monkey the cortical area in which the local application of the drug produces symptoms of hyperesthesia covers not only the entire parietal lobe, but also the precentral regions as far forward as the arcuate sulcus. It includes areas 4 and 6, which are important motor projection areas, as well as areas 3, 1, 2, 5 and 7. The symptoms of sensory excitation indicate that the cutaneous sensibility of both sides of the body is represented in each cortex, while deep sensibility is chiefly represented in the contralateral cortex. The action of strychnine fails to bring out the detailed localization which other methods have revealed; the cortical zone is divisible only into leg, arm and face areas. The application of strychnine to a few square millimeters within any one of these three gives rise to the same hypersensibility as strychninization of any other similar fraction of that area. Dusser de Barenne has always explained this on the basis of the assumption that strychnine causes a spread of excitation through the whole of the area, and recently in work with McCulloch[9] he has secured direct evidence of the correctness of his explanation. As Dusser de Barenne has pointed out, strychnine in bringing out the maximum of sensory function obscures the finer functional differentiations. This is the chief limitation of the method. It has, however, delimited a large area into which, it is reasonable to suggest, future work will have to fit the details, functional and anatomical, of the total cortical representation of each modality of somatic sensibility.

The problem of the representation of somatic sensibility in the cerebral cortex is one which, in spite of more than sixty years of experimental attacks upon it, still demands that attention be given the matter of locus. Until this aspect of the problem has been further elucidated it is likely that considerations of the intimate nature of the cortical

mechanisms involved will prove delusive. It was with this point in mind that the experimental work which forms the basis of this lecture was undertaken. Two methods have been employed, one of them old, the other quite new. It was hoped that each might give information bearing on the important question whether the different modalities of cutaneous and deep sensibility have cortical representations which are spatially separate, but in this respect our work to date has been disappointing. I am able, however, to report results which appear to give precise information concerning the locus of cortical mechanisms subserving tactile sensibility.

I. Sensory Components in the Cortical Management of the Placing and Hopping Reactions

The fact that in the monkey certain postural reactions are dependent on the cerebral cortex has permitted the analysis which forms the first part of this lecture. The simplicity of these motor acts, their uniform presence in normal animals and their easy elicitation by specific stimuli make them singularly favorable instruments for the study and delimitation of the cortical control. In the course of a series of experiments designed to delimit the central management of these reactions Woolsey and I[10] have been able to secure certain information concerning the cortical representation of the sensory modalities involved in their elicitation. The responses are the placing and hopping reactions which were first described by Rademaker[11] and which have been further studied in several groups of animals by the lecturer and his collaborators. Of special significance in the present discussion are those placing reactions which are evoked by tactile stimulation and the hopping reactions. The latter are proprioceptive in origin.

The Placing Reactions—A primary requirement for normal standing is that the feet should be placed in the proper position. To a considerable extent the normal monkey accomplishes this through the agency of the following reactions:

1. When the animal is moved toward a supporting surface visual stimuli cause the feet to be put down in such a way that without further adjustment they can support the body in standing. If the movement of the body is downward and sufficiently rapid, vestibular stimuli will bring about a similar response. Although we have made a study of the central control of these visual and vestibular placing reactions, our results are irrelevant for the purposes of the present discussion and will not be given.

The remaining placing reactions can be elicited in pure form only when visual placing is excluded by blindfolding or by removal of the occipital lobes.

2. If the animal is held in the air with legs free and dependent, the slightest contact of any portion of the hand or foot with the edge of a table results in either an immediate

and accurate placing of the palm or sole on the table or a grasping of its edge by fingers or toes. This response is usually followed immediately by placing of the unstimulated opposite hand or foot (cross-placing).

3. If with arms free, the chin, lips, sides of the jaw, or merely the hairs of the face are brought into light contact with some supporting surface both hands are instantly raised and placed on the source of the stimulus. Occasionally the feet are also placed. When the arms are held such stimulation causes the feet to be brought up and placed.

4. When the arms or legs are thrust over the edge of a table on which the animal is standing, lying or sitting they are immediately lifted so that their original position on the table is regained. (Since both tactile and proprioceptive stimuli may enter into the elicitation of this reaction we have not used it in our attempt to solve the problem under consideration.)

5. A proprioceptive placing reaction of the limb may be evoked in animals in which reaction 2 has been differentially abolished by appropriate surgical procedures, e.g., parietal lobectomy. In such preparations contact of the apical portions of the limb with a table edge does not of course evoke placing. When, however, forward displacement of the body has induced a considerable degree of retroflexion at shoulder or hip, the hand or foot is lifted, carried forward and placed far inside the table edge. This is a reaction which Rademaker termed a proprioceptive correcting movement of the limb.

The Hopping Reactions—These are specific corrective movements of the limbs which serve to maintain a standing posture under conditions involving displacement of the body in the horizontal plane. They may be demonstrated by holding the animal so that it stands on one arm or one leg. Then on moving the body forward, backward or to either side, the limb hops in the direction of the displacement so that the hand or foot is kept directly under shoulder or hip. When displacement of the body induces in the limb a deviation from the normal median perpendicular position the supporting tone of the muscles around the proximal joints diminishes, the limb is flexed, moved in the direction of the displacement, and the apical portion put down again to give a median support for the body in its new position.[11] Thus the hopping reactions, like the placing reactions, serve to put the feet in the normal position for standing, but they also contribute to the maintenance of equilibrium. The nature of the postural changes which induce these specific responses suggests that they are proprioceptive in origin. According to Rademaker and Hoogerwerf[12] the adequate stimulus is actually a stretching of one or another group of muscles. Whether or not sense organs in joints or tendons are concerned is a question which has not been decided. Our observation that hopping in the leg can be evoked by body displacement after complete denervation of all parts below the knee shows clearly that these responses are not dependent on contact or deep pressure, but are evoked by stimulation of proprioceptors in the proximal portion of the limb. We feel fully justified in using them as criteria of the operation of a central controlling mechanism which is thrown into action by afferent impulses from proprioceptors.

The Comparative Physiology of the Reactions—In the reptile (alligator, lizard) placing in response to tactile stimulation does not occur, but proprioceptive placing and hopping reactions are present. These depend upon central mechanisms lying below the telencephalon.[13,14] In the rat and rabbit reactions similar to those described above occur, but they are less well developed; on decortication all placing reactions in response to tactile stimulation disappear, but the hopping reactions are only slightly disturbed.[15,16] In the cat and dog removal of cortex produces a similar but more complete deficit.[17,18] Thus in the ascending scale of vertebrate quadrupeds the central control of these particular responses becomes more and more "corticalized." In the subprimate mammals it has been found that the cortical management of the reactions of the legs of one side is spatially limited to the sensorimotor area of the opposite hemisphere; a maximal cortical deficit is produced by ablation of this area alone while removal of all cortex except the

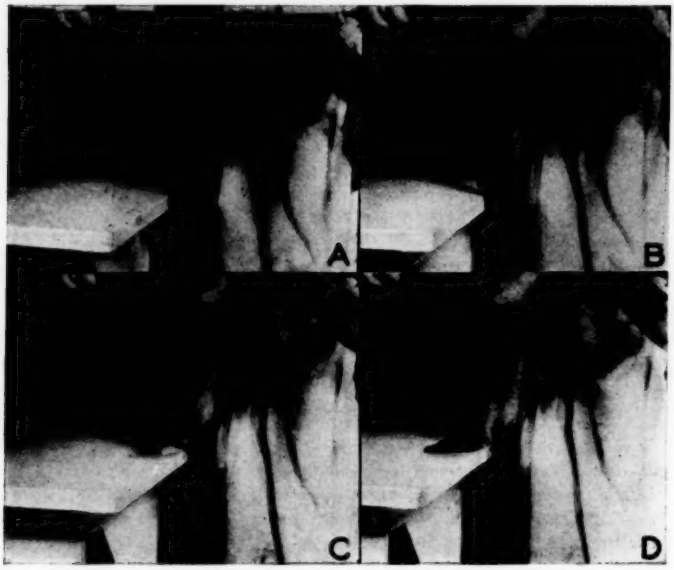

Fig. 1—Four frames from a motion picture film taken fifteen months after removal of areas 4 and 6 of the left cerebral cortex. A-D show stages of the normal placing reaction of the left arm which occurs when the backs of the fingers are brought into slight contact with the edge of a table. Note that the response fails to occur in the arm contralateral to the cortical ablation. (Woolsey and Bard.[10])

sensorimotor zone leaves the responses unimpaired.[15,17] Because of the more highly developed cortex of the monkey it has been possible to extend the study of these reactions beyond the task of delimiting the total area of cortex concerned in their control to an analysis of the respective rôles played by the cortical motor and sensory components.

Experimental Results—After hemidecortication in the monkey all these responses except the labyrinthine placing reactions (which become greatly deficient) are totally and permanently abolished in the contralateral limbs, while those of the ipsilateral extremities remain entirely normal. With this as an established fact experiments were carried out to determine just which cortical areas are concerned. It was found that unilateral removals of (a) all cortex rostral to the central fissure, i.e., the frontal lobe, or (b) areas 4 and 6 together, or (c) the cortex corresponding to Brodmann's representation of area 4, cause enduring loss of all contralateral reactions except the visual and labyrinthine which are

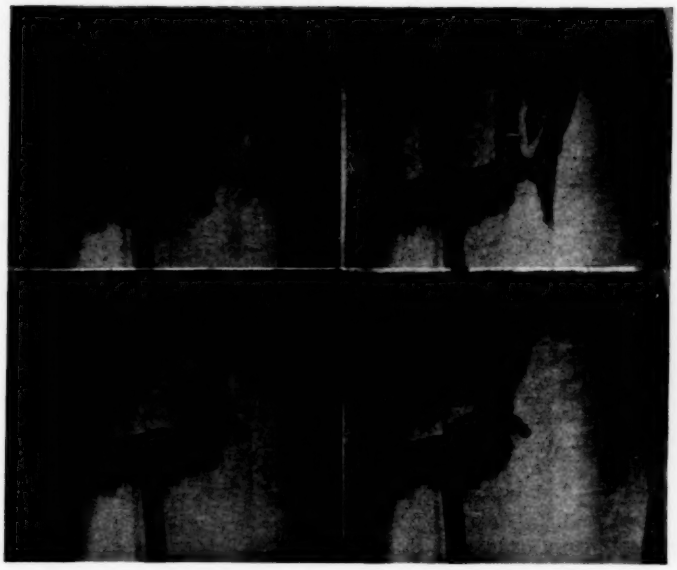

Fig. 2—A contact cross-placing reaction in the monkey shown in Fig. 1. Because of the absence of area 4 of the left cortex the right foot is not placed when it is touched to the edge of the supporting surface, but this tactile stimulus elicits placing of the left foot, a response which, as explained in the text, depends on the integrity of the left postcentral gyrus. (Woolsey and Bard.[10])

retained in modified form. Incomplete extirpations of area 4 (as outlined by Brodmann) or removal of both banks of the central fissure (Poliak's focal sensory zone) produce permanent deficiencies but not complete losses.

When a unilateral *precentral* ablation has produced a complete loss of the placing reactions of the opposite limbs it is still possible (in a blindfolded animal) to obtain placing of the sound (the ipsilateral) hand or foot by bringing the deficient (the contralateral) members into slight contact with the edge of a table. We have termed this response a *contact cross-placing reaction* (Fig. 2). Its occurrence indicates that a light tactile stimulus is appreciated although the motor responses of the stimulated members are completely deficient. Obviously the disappearance of the contralateral contact placing reactions which follows removal of the entire frontal lobe or of area 4 represents a motor rather than a sensory

loss. Since contact cross-placing reactions cannot be obtained after complete hemidecortication it appears that they depend on postcentral cortex. In fact they depend on the postcentral gyrus and it may be supposed that the cortex of this region, on receiving afferent impulses originating at the surface of the contralateral half of the body, somehow brings into action the motor cortex of the opposite hemisphere. To date we have been unable to secure any evidence that there is an ipsilateral cortical representation of the type of sensibility necessary for the contact cross-placing response.

The all-important rôle of the postcentral gyrus in the central mediation of placing reactions evoked by light contact (tactile stimulation) is clearly shown by the results of its removal. After such an operation (also of course after unilateral parietal lobectomy or removal of all cortex except the frontal lobe) an appropriate contact stimulus applied to the hand, foot or jaw of the opposite side causes neither placing nor cross-placing. This loss is permanent and entirely contralateral; the reactions of the ipsilateral limbs evoked from that side remain normal. That the deficiency is not the result of impairment of the cortical motor mechanism is demonstrated by this fact: When the side of the face opposite the intact hemisphere is given an appropriate tactile stimulus while the limbs of that side are held, the limbs contralateral to the ablation engage in a perfectly executed cross-placing response. This reaction is a phenomenon which has permitted us to demonstrate a spatial separation of the motor and sensory components of the cortical mechanisms essential for the placing reactions evoked by tactile stimulation. Cross-placing depends on some functional connection between the postcentral gyrus of one hemisphere and area 4 of the opposite side. It is of interest that complete division of the corpus callosum fails to abolish or in any way to modify the cross-placing reactions.

Although ablation of the postcentral gyrus completely and permanently abolishes the possibility of inducing placing reactions in response to tactile stimulation of the opposite side, hopping reactions are only temporarily if at all affected. After such an ablation and even after removal of all cortex except the frontal lobe they soon return to normal, and then proprioceptive placing can also be elicited. Many experiments have afforded evidence that removal of all cortex lying rostral to area 6 does not affect either hopping or placing. The conclusion that the entire cortical management of these proprioceptive responses is situated rostral

to the central fissure seems justified in view of two additional facts: (a) removal of the second parietal lobe does not affect the reactions and (b) proprioceptive cross-placing cannot be obtained after hemidecortication. If there is a sensory component in the cortical control of the hopping and proprioceptive placing reactions it must be precentral in location and therefore anatomically quite separate from the sensory cortical mechanisms essential for the tactile placing reactions. We have, however, been unable to demonstrate any topographical division of the cortical management of these proprioceptive reactions into sensory and motor parts. The identification of a sensory element here would permit the conclusion that the two types of sensibility (tactile and proprioceptive) involved in these two groups of postural reactions have separate representations in the cortex. Although it seems probable that a sensory element enters into the cortical control of hopping and proprioceptive placing, there remains the possibility that the motor region may act merely by facilitating through tonic efferent discharge a subcortical mechanism and that the withdrawal of this influence on removal of area 4 abolishes these responses by raising the threshold of the subcortical center to proprioceptive impulses.* It is certainly most unlikely that in the evolutionary process which has resulted in corticalization of the control of these reactions the ancient subcortical mechanism apparent in reptiles and discernible in decorticate rabbits, rats and carnivores has been bodily lifted into the cerebral cortex. Indeed its existence in the monkey can be demonstrated. Here, as already mentioned, removal of area 4 or hemidecortication completely abolishes the hopping reactions of the opposite legs; no return is seen during postoperative periods of from one to three years, and in this sense the functional loss is permanent. Yet if in any of these preparations the intact cerebral hemisphere is subjected to an ablation which includes area 4, poor but definite hopping reactions can be elicited at once in the legs contralateral to the original lesion and later in the ipsilateral limbs. Woolsey has observed this phenomenon in a completely decorticate monkey which to date has survived removal of the second cortex for more than four months.

In an earlier communication[17] it has been urged that a true measure of the degree of cortical localization of any function can be obtained only by determining how much cortex may be removed without disturbing the function in question. In attempting to apply this principle to the present

* This possible explanation of the rôle of the motor cortex in the central control of the hopping reactions was first suggested to the writer by Dr. Warren S. McCulloch of Yale University.

problem we found that ablation of all cortex of the frontal lobe lying rostral to area 4 or extirpation of occipital and temporal lobes together has no permanent effects on the hopping reactions and the non-visual placing reactions. When both removals were carried out in the same hemisphere the remnant, consisting of areas 4, 3, 1, 2, 5 and 7, was able normally to control the reactions of the opposite legs. In two animals the subsequent removal of the entire cortex of the other hemisphere did not affect the reactions of the limbs opposite the remnant.

Conclusions—From this study Woolsey and I have concluded that in the monkey the cortical management of those placing reactions which are evoked by tactile stimuli is confined to a zone consisting of the parietal lobe and that portion of the frontal lobe which corresponds to Brodmann's designation of area 4. The cortical motor mechanism essential to the execution of the placing reactions of the limbs of one side is situated in area 4 of the opposite hemisphere. Impulses from tactile receptors in the limbs of both sides and from similar receptors located on both sides of the face can apparently throw this motor mechanism into action, but this effect depends on the integrity of the postcentral gyrus opposite the side stimulated. It is therefore reasonable to conclude that the form of tactile sensibility involved in the elicitation of the placing reactions has a cortical representation which is confined to the postcentral gyrus.

Our results also show that the cortical management of the hopping reactions is situated entirely precentrally and that these responses are independent of all cortical tissue lying outside the frontal lobe. But, as has already been mentioned, they do not permit us unqualifiedly to assert that this cortical mechanism contains a sensory component. That an efferent projection system originating in area 4 is almost completely essential for the occurrence of hopping in the monkey cannot be doubted. The question whether its influence on hopping is exerted through a tonic action on some subcortical center or is the result of its activation by corticipetal impulses originating in proprioceptors is one which cannot be answered by the results of our ablation experiments.

II. The Representation of Tactile Sensibility in the Cortex of the Monkey as Indicated by Cortical Potentials

As already related, the work which Woolsey and I carried out on the central control of the hopping reactions yielded no certain proof that the proprioceptive impulses which induce these responses actually reach

the cortex. About the time that we came to realize this fact we had the good fortune to join forces with Wade Marshall, who, a short time before, had introduced amplifiers and a cathode ray oscillograph into the Johns Hopkins laboratory and had brought with him not only technical competency but also a number of sound and helpful ideas. Together the three of us set out to determine whether a study of evoked cortical potentials might not throw further light on the cortical representation of somatic sensibility. Although we began with the hope that we might settle the question whether touch and muscle sense have topographically separate cortical representations, we were soon diverted by the discovery that our method was capable of revealing in profuse detail a cortical representation of tactile sensibility. For over a year the study of this has constituted the greater part of our joint efforts and only recently have we made rather desultory attempts to solve the original problem. It must be admitted that to date those of our results which bear on the question of the cortical representation of muscle proprioceptors are inconclusive. Consequently, the remainder of this lecture will deal with our more extensive and far more decisive study of the touch representation.[19]

At the time that we began our investigations there had appeared in the literature evidence to show that stimulation of afferent fibers in somatic nerves may induce electrical changes in one or another part of the cerebral cortex and a few observations had indicated that similar cortical responses can be elicited by stimulation of receptors mediating cutaneous or deep sensibility.[20,21,22,23] No one, however, had undertaken a systematic study in which the relationship between the time and place of *both* the peripheral stimulus and the cortical response was rigidly controlled. With arrangements for recording which left no doubt as to whether there was or was not a definite correlation between stimulus and response it was found, first in cats and later in a series of twenty-five monkeys, that the application of discrete tactile stimuli to any cutaneous area produces in the cortex of the anesthetized animal well-localized surface positive waves. These potentials are of such magnitude, show such regularity over long periods of time, and are so decisive in their characteristics that they can be studied with a facility comparable to that enjoyed in studies of the axon potentials of isolated nerve trunks. That our efforts were productive of definite results from the very beginning was, I am sure, largely due to Marshall's insistence upon the use of mechanically discrete stimuli which were brief in duration, low in fre-

quency and near the human threshold in intensity. Thus were avoided the complications attending spatial and temporal dispersion of afferent impulses. Further, this mode of stimulation is strictly physiological, for the impulses which reach the cortex arise in normal fashion from receptors. When a peripheral nerve trunk is stimulated it is no simple matter to make certain that the sensory fibers excited are ones which mediate a single modality, and even if this difficulty be satisfactorily overcome, some doubt must remain whether the centripetal impulses reach the cortex in a pattern which resembles the normal.

Experimental Methods—A brief description of the actual experimental procedure used will give a basis for judging the nature and significance of the results obtained. The animals were anesthetized with pentobarbital sodium (occasionally chloralosan or dial was used). After opening the skull and dura so as to lay bare the greater portion of the external surfaces of one or both cerebral hemispheres the head of the animal was placed in a Horsley-Clarke instrument constructed to carry two electrodes. This arrangement permitted rapid and precise placing of the leads on the pial surface. Exploration of one or the other bank of the central sulcus was carried out after the opposing gyrus (precentral or postcentral) had been carefully dissected away. The medial surface of the cortex was exposed for study by removal of the inner portion of the opposite hemisphere. When this had been done one bank of the sulcus cinguli could be explored after careful removal of the other. The electrodes were made of No. 50 cotton thread drawn through steel tubing and kept wet with Ringer's solution. One electrode was placed at a given point on the somesthetic area, the other on an indifferent region, e.g., occipital cortex. Provided such leads are separated by a distance of one centimeter or more, the position of the "indifferent" electrode has no significant effect on potentials attributable to activity under the other. For observing and recording these changes a capacity-coupled amplifier having time constants of 93 and 500 msec. was used in conjunction with a cathode ray oscillograph equipped with a fluorescent screen of medium persistence. It was found that if the animal's blood temperature was maintained at a normal level and if the portions of the exposed pial surface not under exploration at the moment were covered with cellophane the cortex remained in excellent condition for many hours. Each mapping experiment necessarily consumed from twelve to thirty-six hours, and we have uniformly found that during these long periods the potentials

obtained do not progressively undergo significant reduction or changes in character. In the course of some experiments they occasionally diminished in size or even disappeared for brief periods but reappeared and soon gained their previous magnitude.

Stimulation was applied to hair-covered areas by a small camel's hair brush, to bare regions by the tip of a small von Frey hair or a cat's vibrissa. These objects were mounted on a lever rigidly attached to the moving armature of an electromagnetic device the coils of which were energized by a pulse 3 msec. in duration. This produced a regular, quick, to-and-fro movement which, at the end of the lever, amounted to a displacement of approximately 0.5 mm. within a few milliseconds. Arrangements were such that the movement of the stimulator occurred at a given and adjustable point on the x-axis line of the cathode ray tube. Thus a clear signalling of the exact time of stimulation was assured. It was found that the application of the stimulator to the skin of a human subject gave a sensation of very light touch which was just above the threshold.

Characteristics of the Evoked Cortical Potentials—With the active electrode on a cortical spot corresponding to the peripheral area stimulated a distinct surface-positive wave follows each restricted tactile stimulus. Even when "spontaneous" cortical waves interfere with the simplicity of the record the procedure described above usually enables one to determine the presence or absence of a correlated response. Nevertheless, the "spontaneous" activity does make this determination difficult, and we have therefore ordinarily worked at a depth of anesthesia which gives a reasonably quiet base line, but does not seriously reduce the magnitude of the induced response. Under these conditions the amplitude of a maximal potential usually lies between 100 and 300 microvolts. The rising phase occupies from 3 to 6 msec., the falling phase from 10 to 80 msec. In the monkey the latencies, in milliseconds, average 15 to 20 for toes, 8 to 11 for fingers, and 5 to 9 for face. These values may fluctuate as much as 20 per cent, but are usually constant within 5 per cent.

We have routinely employed a stimulation frequency of not more than one a second. The discrete surface positive type of response with which we are dealing decreases in magnitude as the frequency is increased and it disappears at rates of from 12 to 15 a second. This effect is apparently related to an interesting masking phenomenon which we have encountered. It can readily be shown that a given cortical spot may yield potentials of approximately equal sizes when a discrete tactile stimulus

is applied successively to different points on a restricted peripheral area. Thus brush stimulation of a few hairs within an area on the arm one inch wide and two or three inches long will evoke potentials from a specific spot. These potentials, however, are attenuated or obliterated if another camel's hair brush is applied with a continuous motion anywhere else within that particular skin area. If the secondary stimulation is applied beyond the boundaries of an area represented at the cortical spot it has no such masking effect.

The extinction of the potentials when relatively low frequencies of stimulation are used suggests the development of a long refractory period somewhere in the central mechanisms which respond. Recently Marshall[24] has investigated this phenomenon. In a series of experiments on cats under deep pentobarbital sodium or dial anesthesia one electrode was placed in the lemniscus, a second in the thalamic radiations and a third on the sensory foreleg area of the cortex. The absolute and relative refractory periods (A.R.P. and R.R.P.) were then determined in terms of the potential responses at each electrode to pairs of tactile or light electrical stimuli applied to the contralateral forefoot. The A.R.P. for the lemniscus was found to be less than 5 msec. while the second response dropped out in the radiations and the cortex at stimulation intervals as long as 50-60 msec. and here the R.R.P. was found to be more than 200 msec. In a second group of experiments on monkeys the cortical responses to weak electrical stimulations of a digit were studied first with the animal under deep ether, then after complete emergence from the anesthetic and finally under deep pentobarbital sodium anesthesia. Multiple electrodes mounted in trephine holes served as leads. With deep ether the A.R.P. is approximately 16 msec., the R.R.P. 72 msec. In the absence of anesthesia the A.R.P. is only 4 msec. and the R.R.P. is about 17 msec. But when administration of pentobarbital sodium has resulted in full surgical anesthesia the A.R.P. becomes approximately 38 msec. and the R.R.P. occupies an interval of 500-700 msec. These two groups of findings suggest that anesthesia, especially barbiturate anesthesia, tends to block ascending impulses by prolonging the refractory period of thalamocortical neurons. Depths of anesthesia which nearly abolish the spontaneous waves do not significantly affect the amplitude or the latency of the first of a series of evoked responses. A very deep anesthesia, however, does markedly reduce the amplitude.

Restricted tactile stimulation of a specific peripheral locus elicits

responses over a cortical area of several square millimeters, but one or more spots of maximal potential are always found. The site or sites of these can be determined only by moving the electrode in steps of a fraction of a millimeter. The size of the cortical area varies with the part of the body surface at which the stimulus is applied. Stimulation within a region of relatively low sensibility, such as the back, gives rise to potentials which are limited to a very small cortical area. In this case the maximally active spot may be no larger than the effective area of the electrode and it is not uncommon to find that the potential drops to 5 or 10 per cent of maximum when the lead is moved only 0.5 mm. In general the potential decreases somewhat less abruptly in certain directions than in others. When the cutaneous area stimulated is one where tactile sensibility is acute, e.g., the skin of the thumb, the potentials appear over a different but very much larger fraction of the cortical somesthetic area. Further, wherever this is the case, there are two or more spots of major potential situated along a more or less definite strip of cortex. Although the potentials at these spots may be of nearly equal sizes there is usually one which shows a shorter latency than the others; at the other spots the longer latency appears as a 2 to 5 msec. shift in the entire wave. The fact that in any cortical area the potentials decrease much more precipitously when the electrode is moved in one direction than in another indicates the part played by purely physical spread. In general our experience suggests that within any area potentials greater than 10 per cent of the maximal are physiologically significant if they occur at distances greater than 1 mm. from the maximal point.

At present little can be said concerning the origin of these evoked cortical potentials. The application of Dusser de Barenne's[25] method of thermocoagulation indicates that at least the outer layers of the cortex are not essentially concerned in their elaboration. It is possible that they represent the summed action potentials of the terminations of thalamocortical neurons. On the other hand, they may arise in the somata of cortical neurons. The solution of this fundamental question must await the securing of data more pertinent to it than any at present available.

The Topography of the Cortical Representation—A general mapping of the entire Rolandic region of one hemisphere can be achieved in a single experiment on a monkey by exploring the entire body surface with the stimulator each time the active electrode is placed on one of a series of arbitrarily selected points. This, however, requires a very long period

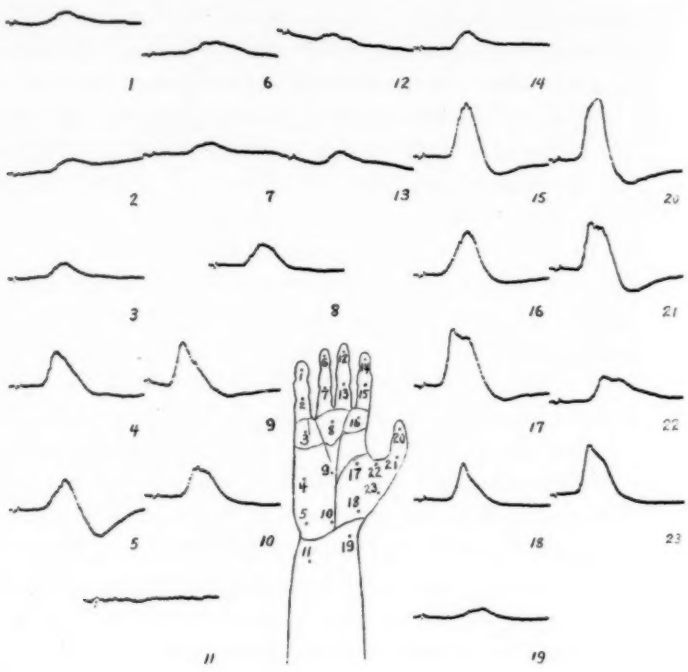

Fig. 3—Surface positive potentials recorded from a single spot in the hand area of the left postcentral gyrus when a light tactile stimulus is applied to various points on the palmar surface of the right hand. Monkey under pentobarbital sodium anesthesia. Recording by cathode ray oscillograph. Small initial deflection signals brief contact of stimulating hair with skin. [Marshall, Woolsey and Bard (From *Macleod's Physiology in Modern Medicine*, 8th ed.).]

of time and is bound to leave many significant areas unexplored. Therefore in the majority of our experiments we have limited our attention to one or another portion of the total cortical representation. Thus a detailed picture is obtained by testing in the manner just mentioned cortical spots which lie only a millimeter or less apart along longitudinal and transverse coördinates. Fig. 3 shows the potentials recorded from a single spot when light tactile stimuli are applied to various points on the palmar surface of the hand. It is evident from the sizes of the waves that the thumb and adjacent surfaces of the palm and index finger are represented. A number of the smaller waves are undoubtedly due to physical spread from nearby cortical spots. A slight change in the posi-

tion of the electrode will always alter the size relationships of the waves of such a group to one another, and with a shift of several millimeters the electrode will fail to pick up any potentials when the hand is stimulated, for it will now be on the locus of the representation of some other region.

The two parts of Fig. 4 illustrate the combined results of mapping experiments carried out on five monkeys. The representation of the tactile sensibility of the body surface shown by the cortical potentials is a very stable arrangement. No shifting of points occurs in the course of an experiment of thirty or more hours. Furthermore, the detailed map of an area derived from one animal is almost identical with that from any other monkey as regards the relationship of different points to one another. Because the form of individual sulci and their relationships to one another vary somewhat, the position of any group of points tends to vary from monkey to monkey in respect to these surface markings. This is particularly noticeable at the rim of the hemisphere. In one animal the representation of the great toe may lie just at the rim, while in another it may be situated on the dorsolateral surface of the cortex 6 mm. from the rim, but in both it occupies the same position relative to the representation of any other part.

The representation of tactile sensibility revealed under the conditions of our experiments appears to be confined to the fields 3, 1 and 2 of Brodmann. No evidence of bilateral representation of this modality was secured except very occasionally in the case of the face. In a number of

LEGENDS

Fig. 4, *A* and *B*—Tactile sensory area of monkey's cerebral cortex as indicated by cortical potentials. In each of the small figures (consisting of a pair of hands, arms, feet, etc.) is shown by shading the cutaneous area which on tactile stimulation gives rise to potentials at the cortical spot indicated by the position of the small figure on the larger diagram. In each case (except the head) the right half of the figure represents the dorsal surface, the left half the ventral surface of the part illustrated. Largest potentials were evoked by stimulation of the central portions of the solidly shaded areas. *A* and *B* each show approximately one-half of the total area. Their positions with respect to the general topography of the cortex are indicated in the inset which is a diagram of the dorsolateral and medial surfaces of the left hemisphere. *a*, central fissure; *a'*, bottom of central fissure; *b*, intraparietal sulcus; *c*, postcentral sulcus; *d*, rim of hemisphere separating medial and dorsolateral surfaces; *e*, sulcus callosus marginalis; *e'*, bottom of sulcus callosus marginalis. Stippled areas are the posterior bank of central fissure and superior bank of sulcus callosus marginalis. The small figures are of such size that each would cover one square millimeter of cortex if the entire diagram were reduced to actual size. [Marshall, Woolsey and Bard (From *Macleod's Physiology in Modern Medicine*, 8th ed.).]

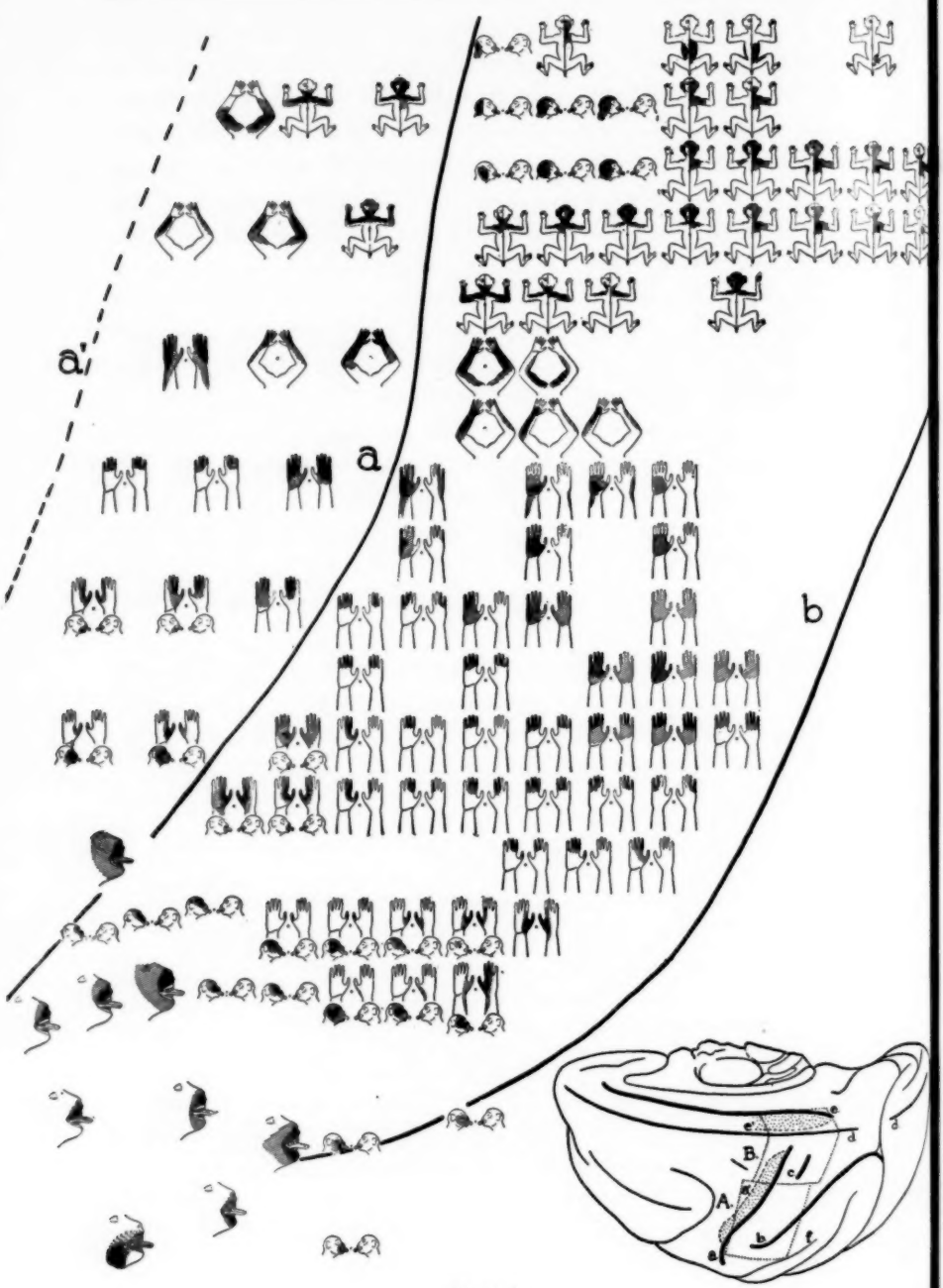

Fig. 4 A

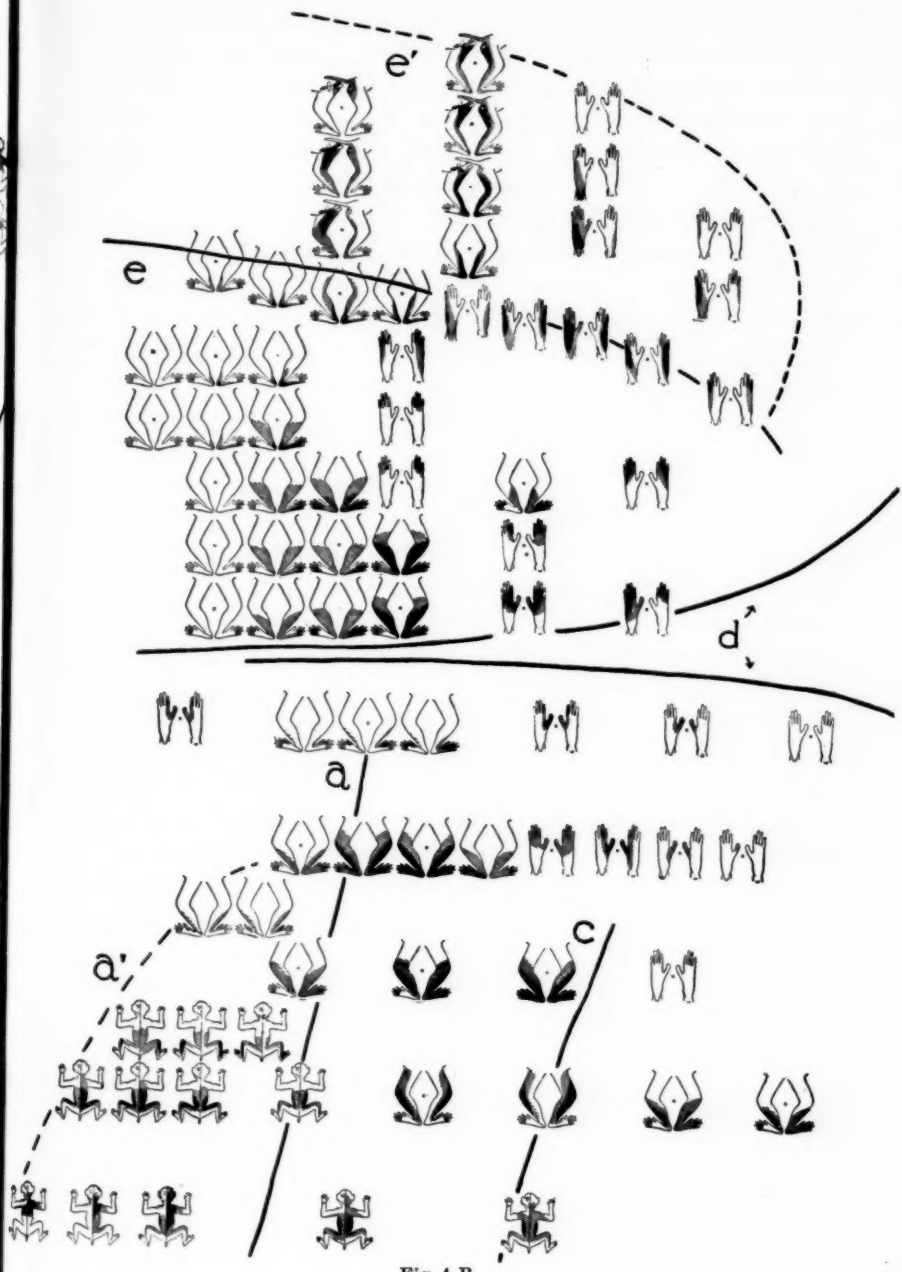

Fig. 4 B

experiments a brief pressure stimulus (given by applying the lever-arm of the stimulator to a part) evoked rather weak potentials in the somesthetic area of the ipsilateral cortex, but in these cases it was never certain that vibrations set up by the stimulus were not transmitted to the opposite side of the body where they might easily act as adequate tactile stimuli. No maximal potentials in response to tactile stimulation were ever found precentrally. On following a longitudinal coördinate forward small waves were usually picked up from points just anterior to the central sulcus, but these are probably the result of physical spread from the most anterior parts of the postcentral gyrus. They were never encountered in animals from which the adjacent portion of the postcentral gyrus had been extirpated some time previously.

Inspection of Fig. 4 shows that the representation of each part tends to occupy a narrow strip of cortex which runs diagonally to the sagittal plane. These "diagonals" extend in a posterolateral direction from the central sulcus. Up the postcentral gyrus to the hemispheral rim and then down the medial surface and on to the upper bank of the sulcus cinguli the parts of the contralateral body surface are represented in an orderly sequence. For all portions of the body caudal to the arms the cortical sequence clearly reflects the metameric origin of the dermatomes. This is especially striking in the case of the leg, where the preaxial (dorsal) surface is represented, from hip to hallux, on the dorsal aspect of the hemisphere, while the postaxial (ventral) surface, including the remaining digits, is represented, from toes to hip, on the medial aspect of the hemisphere above the points for perineum and tail. The order is that of the sensory spinal skin-fields as determined by Sherrington[26] for the hindlimb of the monkey. The sequence—hip, leg, foot, toes—shown in charts derived from the results of direct electrical stimulation of the human sensory cortex[5,6] is, in the light of the work with cortical potentials, a limited and only partly correct one. This defect is of course chiefly due to the difficulties which attend exploration of the medial cortical surface during neurosurgical procedures on man. A feature of the sequence disclosed by the evoked potentials which was unexpected and appears to be new is that the head, as well as the neck, is represented between the areas for arm and body. In this region even the face appears to have some slight representation. The face area proper, however, is situated near the lower (lateral) extremity of the postcentral sensory zone.

Before the representation of tactile sensibility had been mapped by the method of cortical potentials Woolsey and I made some attempts to abolish, by means of limited postcentral ablations, the possibility of eliciting placing in response to tactile stimulation of a hand or a foot. After these operations some of the animals showed what might be called "recovery of function." As a matter of fact we lacked at that time any precise criterion of the sensory areas for hand or foot; we could only proceed on the assumption that they were situated directly across the central sulcus from the corresponding motor points. We were of course unaware of the diagonal arrangement of the representation of a part. It can be said, however, that subsequent reference to the maps has indicated that in every case of partial "recovery" the postcentral ablation had been incomplete. More recently we have been able to correlate in one and the same animal the sensory loss determined by a study of the contact placing reactions with that indicated by the method of exploring the cortex for evoked potentials. The results obtained in one monkey are especially instructive. In this animal a segment of the postcentral gyrus lying just above the end of the intraparietal sulcus was removed. Throughout a postoperative period of several months the contralateral hand was regularly placed when the thumb was brought into light contact with the edge of a table, but no placing occurred when this same tactile stimulus was applied to the ulnar side of the hand or to the forearm. Before sacrificing the animal its cortex was examined for potentials in response to tactile stimuli. It was found that the ablation had spared a large fraction of the thumb area, but had almost completely removed the representation of the tactile sensibility of the rest of the upper extremity.

Discussion and Conclusion—It must be recognized that in all probability this method does not reveal the entire cortical representation of tactile sensibility. It seems likely that the area within which the evoked potentials have been found is that which receives those thalamocortical fibers which convey impulses originating in tactile receptors. In other words, it is a sensory projection area. Whether the projections from the thalamus to parts of the cortex other than areas 3, 1 and 2 are concerned with tactile sensibility is a question which cannot at present be answered conclusively. It may be pointed out, however, that the anatomical studies of Walker[3] suggest that the part of the thalamus which receives the majority of the fibers of the medial fillet and spinothalamic tracts projects almost entirely upon the cortex of the central sulcus and the postcentral gyrus.

In any consideration of our results the question of the effects of the anesthesia must be given attention. Anesthesia doubtless represses spread of impulses through the cortex and possibly it differentially blocks the entry of tactile impulses into the ipsilateral cortex. In a number of experiments in which several multiple electrodes were mounted in the skull, thus making it possible to record the potentials in the animal after emergence from the anesthetic, evidence has been secured that the anesthetics used do not significantly modify either the form or the locus of the potentials evoked by tactile stimulation. In these experiments without anesthesia we have been unable to demonstrate an ipsilateral representation of the tactile sensibility of the body.

In conclusion it may be stated that this study, based on receptor stimulation and correlated electrical response, has shown that the tactile sensibility of each part of the body is represented in profuse topographical detail over the postcentral gyrus. It does not follow that the total cortical response to a tactile stimulus is confined to this area. It is reasonable to suppose, however, that whatever that response may be it is based on the highly stable anatomical substratum which has been functionally demonstrated in terms of evoked cortical potentials.

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THE PRESENT STATUS OF GYNECOLOGIC ENDOCRINE THERAPY

HOWARD C. TAYLOR, JR.

GYNECOLOGIC endocrine therapy has enjoyed an extraordinary development in the last few years. It is only a decade since the only available endocrine products from the ovary or anterior pituitary were desiccated extracts, now regarded as quite inert, but which the gynecologist optimistically made use of. Since then, glandular preparations of three or four major types, each in several forms with varying indications, have become available. Yet it is almost universally recognized that the rapid expansion in the clinical use of these substances has been accomplished at some sacrifice of soundness and sincerity.

The reasons for the vogue which endocrine therapy is enjoying are not hard to find. First, there is the undoubted need for a scientific therapy of the many functional disorders of the female reproductive system. Furthermore, the so-called sex hormones are apparently relatively safe, more or less regardless of dosage, and no accidents have occurred, such as attended the introduction of insulin, thyroid extract or pituitrin. That a certain artificial demand has been created by an advertising campaign to the physician is also probable.

Yet the most important reason for the acceptance of the new products is the brilliance of the basic scientific work which preceded their appearance in the clinical field, for whatever may be said against the new endocrine therapy, it can never be said that it is entirely empirical. The soundness of the reasoning which leads to the prescription of certain gland products is often so good as to make the physician biased in the evaluation of his results. To this sound physiologic background must be added the helpful but misleading fact that gynecologic endocrine dysfunction has a great tendency to spontaneous improvement. A series of optimistic reports has, as a result, led to a rapid approval of the endocrines for many conditions for which more critical judgment may eventually question their value. Any attempt at present to delimit the field of gynecologic endocrine therapy is bound to be tentative and to lead to conclusions which will be unacceptable to many. Nevertheless

such provisional accounting may occasionally be useful.

In the following pages, the subject of gynecologic endocrine therapy will be considered under the following heads:

(1) The endocrine agents now available for affecting the female pelvic function and their physiologic action.

(2) The diagnostic methods available to determine the physiologic nature of the disturbance underlying the patient's clinical symptoms.

(3) A classification of the conditions for which the so-called sex hormones have been advised into categories of relatively proven usefulness.

I. The Available Agents

The agents available for affecting the endocrine status of the female reproductive tract fall into several groups. First are those which in a measure reproduce the function of the ovary itself by acting upon the secondary organs, the uterus, vagina and breasts. This group includes the various estrogenic substances and the specific hormone of the corpus luteum. Second are the substances which affect the ovary and are therefore classed as gonadotropic. They are a somewhat miscellaneous group, both as regards their origin and action. Third, there is the hormone of the thyroid gland whose action on the pelvis is not definitely understood, but whose clinical effectiveness for some conditions seems established. Finally, there is radiation therapy, which as a rule has the opposite action from that of most of the hormones, namely, to reduce rather than increase function.

A. THE ESTROGENIC HORMONE

Estrogenic substances are available for therapeutic use in several forms. The substance most widely employed is probably estrone or ketohydroxyestrin, known to the profession by the terms theelin, folliculin, amniotin, menformon and others. A closely related substance is estriol or trihydroxyestrin, sometimes called theelol. This latter product is somewhat less active than estrone, but has been believed to be more efficient as a preparation to be given orally. A material intermediate in chemical formula between estrone and estriol is estradiol or dihydroxyestrin. This substance has been combined with benzoic acid to form estradiol benzoate, marketed under the commercial names, progynon B or oestroform B. This compound has the property of being more slowly broken up in the body than are the simpler estrogens, and has there-

fore the advantage of a more prolonged effect. A fourth estrogenic substance is the one commonly known as emmenin (Collip[1]), and thought to be estriol in a combined form, probably estriol glucuronide (Cohen[2]). It is much less active than are the "free estrogens", perhaps especially in the absence of an ovary, the site of its supposed transformation to a more potent form. It is recommended, however, as a substance especially available for oral administration.

Great confusion has resulted from the fact that the clinician has been subject to a constantly changing nomenclature of dosage, namely mouse units, rat units, and now, unexpectedly, international units. The present unit, accepted by a committee of the League of Nations, is perhaps relatively permanent. This "international unit" is the equivalent of one ten-thousandth of a milligram (0.1 gamma) of a crystalline preparation of estrone. The relation of the animal units to this gravimetric unit is actually quite variable, depending on the method of bio-assay, but a mouse unit is usually accepted as about equal to one international unit, a rat unit to five international units.

Although the use of estrogenic substance has a certain rationale, the dosage for most of its indications is largely empirical. This is obvious when it is remembered that except in the case of the menopause, the degree of ovarian deficiency which must be compensated for by therapy, is unknown. A start toward the development of a rational dosage has been made chiefly in reference to the menopause. Kaufmann[3] in 1932 showed that artificial menstruation could be produced by a dosage of 210,000 mouse units of progynon benzoate followed by 35 rabbit units of corpus luteum. This is apparently the basic requirement for the building up of an endometrium sufficient to cause bleeding. Such a result, however, is unnecessary in usual therapy and the goal is more generally simply the suppression of the excessive anterior pituitary activity which is associated with hot flashes. Frank, Goldberger and Salmon[4] have reported the disappearance of the gonadotropic factor from the urine, the alteration of the vaginal spreads and the disappearance of menopause symptoms when 4,000 rat units are given every other day for two weeks. Thus their figure for the suppression of gonadotropic activity in a woman without ovarian tissue is 120,000 international units of estradiol benzoate in two weeks time. Papanicolaou and Shorr[5] had found that it took from 250 to 300 rat units daily to induce complete changes in the vaginal smear, and with oral administration fifteen to twenty times this dose.

Other workers (Werner[6]) have, however, placed the figures somewhat lower and have noted stimulation of the breasts, endometrium and vagina with as little as 5,000 to 10,000 international units. Using a different method of study, that of following urinary excretion of the estrogens, Mazer and Israel[7] noted that an injection of 1,000 rat units in castrated women produced normal levels for four days. Larger amounts, such as 5,000 to 10,000 rat units, produced a temporary hyperestrinism which fell to a normal level by the fourth to fifth day.

The use of estrogenic substance for any purpose in women who have sufficient ovarian function to menstruate does not give dependable results. Since the basic ovarian function which the menstruating patient possesses is difficult or impossible to gauge, the additional estrogenic substance which must be added to raise the theoretically low level to a theoretical normal is the purest guess work.

The functions of the estrogenic hormone which are invoked to support its use in therapy are briefly the following:

(1) To stimulate proliferation of the mucosa of the uterus, vagina and mammary glands and to a certain extent the muscular walls and supporting stroma of these organs. This function is the basis of the treatment of amenorrhea and hypomenorrhea due to deficient development of the endometrium, of dysmenorrhea supposedly due to deficiency of the myometrium, and of senile and juvenile vaginitis.

(2) To increase the sensitivity of the uterine musculature. This function has given rise to little definite therapy, although the estrogens have been suggested in the therapy of missed abortion and postmaturity in obstetrics.

(3) To suppress excessive activity of the anterior pituitary gland. Continuous small doses of estrin have apparently found a definite place in the therapy of the menopause. A somewhat paradoxical effect may, however, be produced when very large doses of an estrogen are given and, instead of a suppression, a temporary increase in gonadotropic activity, especially in its luteinizing function, may result. This reaction may be at the basis of successful therapy of amenorrhea with large doses of estrin.

The dangers of estrogen therapy are, like its uses, somewhat theoretical. The experience of research in mammary gland cancer in mice, where the ovarian hormone undoubtedly is a factor in bringing out latent tendencies to cancer in susceptible strains, leads to some anxiety

as to the effects of the too indiscriminate use of this agent. Mammary carcinoma developing during or after estrogen therapy is sometimes heard of, but such a coincidence must of necessity occasionally occur in view of the frequency of spontaneous breast cancer. Depression of the pituitary, and indirectly of the ovary, by long-continued injections is theoretically possible (Clauberg and Breipohl[8]). Immediate reactions associated with swelling of hands, face and eyes have been noted (Klaften[9]) and unexpected uterine bleeding is not unusual.

B. CORPUS LUTEUM HORMONE

Desiccated tablets of corpus luteum gland have been in use for a long time, but it is only a few years since active preparations have been available. The names under which the hormone passes include progestin, progesterone, corporin, proluton, lipolutein and many others.

The question of units is again a confusing one. Two biologic units have been tried, one based on the use of an adult, the other on an immature female rabbit. The former gives the American or Corner-Allen unit, which is about twice the size of the Clauberg or European unit (Young[10]). More recently an international unit has been introduced, which is the equivalent of one milligram of pure crystalline progesterone. This unit is a little larger than the Clauberg rabbit unit, considerably smaller than the Corner-Allen unit. It is well to remember that an international unit of corpus luteum is one milligram, an international unit of estrone one ten-thousandth of a milligram, for otherwise the respective doses of the two substances seem completely out of harmony.

The dosage of corpus luteum hormone is again largely empirical. In castrated women Kaufmann[3] found that from 35 to 90 rabbit units (Clauberg) needed to be added to change a proliferative phase produced by estrogenic substance to a truly secretory endometrium. On the other hand clinical results have been reported in dysmenorrhea with dosages varying from 2/25 to one rabbit unit.

The functions of the corpus luteum hormone upon which therapy is based are the following:

(1) The transformation of a proliferative to a secretory type of endometrium. This effect leads to the use of the hormone in cases of bleeding due to a hyperplasia of the endometrium, and perhaps also in sterility when theoretically due to a deficient corpus luteum preparation of the endometrium.

(2) The control of nidation of the ovum. This function is bound up with the one just mentioned, for the protective effect of the corpus luteum on early pregnancy is in all likelihood the stimulation of early decidual development. The loss of the corpus luteum early in pregnancy is well known to result in abortion, and the hormone has accordingly been given in threatened or habitual abortion on the theory that a natural deficiency in the patient is to be remedied.

(3) Reductions in sensitivity of uterine musculature. Repeated observations and experiments have indicated that under the influence of progestin the uterine musculature becomes less responsive to certain stimuli, such as pituitrin, and that the uterus of certain animals is less active during times when corpora lutea are present. In this respect the effect of progestin is antagonistic to that of estrin. This function has been used to build up a corpus luteum therapy of dysmenorrhea. The same rationale can be found for its use in after pains following labor.

In general, progestin has been available until very recently in amounts too small for its wide trial in physiologically effective doses. No deleterious effects are yet recognized, beyond possibly a disturbance in menstrual rhythm or in the amount of flow.

C. THE GONADOTROPIC HORMONES

There are certainly several substances which affect the ovary and the testis and it is of primary importance to recognize the essential differences in their actions. Two effects on the ovary are of possible clinical importance, the stimulation of follicle growth itself and the luteinization of follicles already present. The former function is, in general, predominant in substances derived from the urine of women in the menopause and from the pituitary gland itself, the latter in products derived from the urine of pregnancy and from the placenta.

(1) The true anterior pituitary hormone is essentially follicle-stimulating. This or related substances have been variously styled FSH (follicle-stimulating hormone), maturity factor, prephysin and gonadogen and prolan A. Even substances within this group undoubtedly differ from each other in their physiologic effects, depending upon their source.

The units of measurement of the follicle-stimulating hormone depend upon the production of mature follicles in the ovary of an infantile rat or mouse or upon an accepted percentage increase in the weight of the ovary or of the uterus. The clinical dosage is quite undetermined, and

it is possible on account of the scarcity and expense of the material that practically all recommended or reported doses have been insufficient to produce true clinical effects.

The use of the follicle-stimulating hormone is based on its known effect in causing development of the ovary and follicle formation. On account of this it may logically be used in any condition of known hypo-ovarianism and its secondary genital underdevelopment. It is perhaps especially indicated in sterility due to failure of normal ovulation.

(2) The gonadotropic substances derived from pregnancy urine have been called APL (anterior-pituitary-like), prolan B, antuitrin S, antophysin and follutein. The standard on which this substance is measured is based upon the production of corpora lutea in immature rats or sometimes in mice.

The dosage here is again still on an empirical basis but the supply of this hormone is sufficiently great to have permitted the trial of a wide range of dosage. Novak and Hurd[11] reported success with 200 rat units daily in cases of functional bleeding. Kurzrok[12] advises 750 rat units daily in cases of severe bleeding. On the other hand, Hamblen[13] failed to find evidence from endometrial biopsy that ovulation or corpus luteum formation had occurred after total doses of 6,000 to 24,250 rat units in daily amounts of 400 to 8,000 units.

On account of its known luteinizing effect on the immature ovaries of mice, the luteinizing hormone is recommended clinically whenever the corpus luteum is theoretically deficient. Thus it is advised especially in cases of dysmenorrhea and functional uterine bleeding. For the latter, a direct effect on the endometrium itself has also been claimed. The substance is likewise used, although probably without a sound theoretical basis, for various types of ovarian underfunction.

(3) A third hormone of the anterior pituitary is thought to stimulate secretion of the mammary gland. The substance is measured in so-called bird units, depending upon its effect on the crop glands of pigeons. It has been available as prolactin and has been used to stimulate the secretion of milk in the postpartum period (Kurzrok, Bates, Riddle and Miller[14]) and in chronic mastitis (Lewis and Geschickter[15]).

The dangers of the use of the gonadotropic substances are not known, and are probably not great. On account of the fact that these are complex molecules and are not yet available as pure products, local and general reactions sometimes occur. The luteinizing substance is not be-

lieved to have a simple physiologic effect on human ovaries, and abnormal cystic follicles may be produced (Geist[16]). Certain defects produced in the offspring of mice injected with this material have led at least two observers to suggest that anterior pituitary hormone should not be given during the child-bearing period (Wolff[17]). The contraindications based on animal experimentation have probably about the validity of indications on the same basis.

D. RADIATION OF THE OVARY

It is perhaps unconventional to include radiation under the heading of endocrine therapy, but this is actually a most precise and effective method of influencing ovarian function. The small dosage of radiation usually employed in gynecologic work shows that it is the ovarian effect which is depended upon in practically all indications, except in the control of malignant tumors.

It is possible to produce certain different effects upon the ovary by varying the radiation dosage. A large dose will permanently suppress the ovarian function by destroying all the follicles, while one which is somewhat smaller, 28 per cent of a skin erythema according to Wintz[18], will cause a temporary amenorrhea by injuring only those approaching maturity. That a still smaller dose has a "stimulating" effect is a possibility raised by certain reported successes in the treatment of amenorrhea and sterility.

The disadvantages of radiation therapy are well known. The disappearance of the original symptoms almost always coincides with the appearance of the symptoms of the menopause. Where a temporary amenorrhea is attempted, the chance of it becoming permanent must be accepted. The possibility of damage to the germ plasm, on the other hand, must be thought of when conception occurs after a temporary amenorrhea. In spite of these objections the place of radiation of the pelvis in the endocrinologic field is assured. The invariable control of functional uterine bleeding in women approaching the menopause is alone a more brilliant endocrine success than anything attained by the injection of hormone substances.

Radiation of the pituitary either to diminish or stimulate function has a much less recognized position. The doubt which usually exists as to the actual relationship of the pituitary to the symptoms, the uncertainty as to dosage, the unknown effect on brain structure, and the not

infrequent loss of hair, combine to make this an unacceptable procedure except in research clinics.

E. THYROID EXTRACT

Thyroid extract must be mentioned in any list of endocrine agents affecting the pelvis. The exact nature of its action on the genital organs is unknown, but the clinical fact of disturbances in the reproductive functions in association with thyroid disease is well established. The frequent reports of thyroid extract successfully used to control pelvic dysfunction, especially in patients who have a low basal metabolism or who are overweight, demands its early consideration in all such cases.

II. Diagnostic Procedure in Gynecologic Endocrine Therapy

It would be an enormous aid to intelligent therapy if there were satisfactory means of measuring the activity of the ovary and pituitary gland and actually determining the type and degree of dysfunction from which a patient with given symptoms is suffering. Actually, although such terms as "hypopituitarism" and "hyperestrinism" are rather commonly used, they are based largely upon supposition.

Certain tests to measure the function of the ovary and anterior pituitary have, it is true, been in use for some time and are constantly being improved. They represent a thoroughly sound approach to the problem, but one which has as yet limited practical applications. The tests are apt to be overlooked by the majority and perhaps overestimated by the remainder of the profession. A simple attention to details of the history and physical examination will in many cases give as much information as can be obtained. Under certain circumstances, however, a few additional procedures may be of great value.

A. THE HISTORY

Here the patient's age, the evidence of fertility as derived from the dates of her pregnancies and the use of contraceptives, as well as changes in weight, are of fundamental importance. The menstrual history, however, deserves the greatest consideration. It is well to remember that the changes in the timing of the periods must always be ascribed to a deviation from the normal ovarian function in the form of delays or accelerations of the development of the follicle or corpus luteum. Changes in the amount and duration of the flow, especially if this be in

the form of an increase, are much more apt to be due to local causes in the uterus than to a glandular disturbance.

B. THE PHYSICAL EXAMINATION

The physical examination is also of obvious value. The state of the patient's nutrition, especially if there has been a recent pronounced increase or decrease in weight, has a great bearing on pelvic glandular function. Peculiar distributions of fat and hair, although written and talked of considerably, appear to be of little importance unless the degree of deviation from the normal is very marked. A rough gauge of the patient's constitutional degree of reproductive development may be obtained from noting the size of the breast and nipples, as well as the external genitalia, vagina, and uterus. In contrast to this, some idea of existent ovarian function may be obtained by noting the degree of congestion or ischemia of the vaginal and cervical mucous membranes. The palpation of the ovaries may be important, especially if enlarged, and hence probably cystic organs are detected.

C. ENDOMETRIAL BIOPSY

The patient's own endometrium is decidedly the best test object to determine qualitatively, at least, the presence of ovarian and corpus luteum hormones. Fragments of the endometrium are readily obtained without anesthesia by various types of curettes devised for the purpose (Klingler and Burch,[19] Novak,[20] Hoffmann,[21] Rock and Bartlett,[22] Campbell, Lendrum and Sevringhaus[23]). By correlation of histologic sections with the time in the cycle at which the biopsy is taken, the presence and relative durations of the follicular and corpus luteum phases may be determined. The method may be of special value in the classification of amenorrhea and in the detection of a non-ovulatory cycle as the cause of sterility.

D. VAGINAL SMEARS

It has been shown by Papanicolaou and Shorr[5] that smears of the vagina from women in the menopause are made up of leukocytes and of compact, round or oval cells with well preserved nuclei from the deeper layers of the squamous epithelium. The follicular phase of the menstruating woman and the vaginal secretions of a menopause patient adequately treated with estrin are characterized by an absence of leuko-

cytes and of the oval nucleated cells, while in their place are found flat, enlarged cells with small pyknotic nuclei. Numerous intermediate types of smears occur, corresponding perhaps to various degrees of vaginal atrophy. The study of the vaginal smears is of some practical use in determining whether an adequate amount of estrin has been given for the treatment of menopause symptoms, and perhaps for the separation of the so-called hyperhormonal amenorrhea from the common type due to ovarian underfunction.

E. BASAL METABOLISM

A basal metabolism determination is of enormous importance in gynecologic endocrinology. It is one of the few tests which are roughly quantitative, and if abnormal readings are obtained, adequate agents are at hand for their correction. A basal metabolism test is particularly indicated where sterility is present with obesity or abnormal bleeding occurs unassociated with a hyperplastic pattern of the endometrium.

F. BIO-ASSAY OF ESTROGENIC SUBSTANCE IN THE BLOOD AND URINE

This procedure is one of the most interesting of the methods of clinical study of reproductive physiology. Many clinicians feel that the ultimate has been done for the patient with a genital dysfunction when she is referred for "hormone studies." Few realize that the procedure is still largely in the research stage and that unless the tests are performed with exactness and enormous labor and expense, they are of absolutely no value.

The assay of a single specimen of urine for estrin involves several chemical steps and the use of perhaps twenty castrated mice or rats. It must also be remembered that the excretion of estrin is quite variable throughout the menstrual cycle, and that a report on a single specimen may give a quite erroneous idea of the patient's ovarian function. Even four specimens taken at weekly intervals may accidentally strike only the peaks or the depressions in the irregular curve of estrin excretion. It is scarcely possible to avoid, then, some system of continuous study, such as the assay of consecutive 72-hour specimens, throughout the cycle. Such a routine is confining to the patient and the actual cost of the test to the laboratory cannot be less than a hundred dollars. Tests made upon the blood are even less satisfactory, for a mouse unit is rarely present in less than 40 cc. The amount of blood that would be required

practically precludes repeated tests or a quantitative assay.

The indications for such an assay of the estrogenic hormones in practice are at present few. If a patient menstruates, it may be assumed that a definite amount of estrogenic substance is being excreted. Furthermore, enough data have not yet accumulated upon urinary assays to define the range which should be considered normal. Only if very large or very small amounts are excreted can the figure be given much significance. In amenorrhea, the test may be of use in determining prognosis and possibly in avoiding the mistake of treating a rare case of hyperhormonal amenorrhea with estrogenic substance.

G. BIO-ASSAY OF GONADOTROPIC SUBSTANCE

The study of anterior pituitary hormone excretion is often attempted in association with estrogenic assays. It must be remembered, however, that except during pregnancy and in pronounced degrees of ovarian underfunction, the gonadotropic hormones are present in the urine in amounts too small for accurate measurement. Various workers, it is true, have reported gonadotropic hormone in the urine of normal women especially at or near the time of ovulation (Zondek;[24] Katzman and Doisy;[25] Kurzrok *et al*;[26] Frank and Salmon[27]). The results of different workers have varied so much from each other, however, that the test must be regarded as having as yet little value in routine clinical procedures. Certainly the number of units of gonadotropic hormone reported from a laboratory has no absolute significance, and the validity of the entire report depends entirely upon the accuracy and sincerity of the laboratory doing the assay. The field for the tests for gonadotropic hormone in the non-pregnant woman is certainly at present very small. Possibly it may give an indication of the type and prognosis of certain forms of amenorrhea. Other uses for the test may develop with refinement of methods.

H. CORPUS LUTEUM

Corpus luteum hormone cannot be detected in the blood or urine of the non-pregnant patient. For this reason, until very recently, the endometrial biopsy taken shortly before mentstruation has been the only way of determining whether a corpus luteum has been produced. The recent discovery that corpus luteum was excreted in the form of sodium pregnanediol glucuronidate (Venning and Browne[28]), and that this substance could be extracted from the urine and measured, points perhaps

to the development of the most practical of all the tests for the sex hormones. At present the test is merely awaiting its application to suitable series of cases for its clinical value to be determined.

III. The Clinical Indications for the Use of Hormone Therapy in Gynecology

The value of therapy with the ovarian and anterior pituitary hormones has been established to a varying degree for different clinical conditions. For one or two it is to be regarded as almost specific and certainly the first method of therapy to be considered. For another group favorable reports by a number of reputable workers seem to justify its clinical uses, but only after other investigations and procedures have been carried out. Finally, there is a third group represented by a long list of conditions for which endocrine treatment has been tried, often empirically, with occasional successes, often uncritically reported. Hormone therapy for the latter group should probably be restricted to series of cases under scientific study or resorted to in the individual patient only after all other therapeutic measures have failed.

A. Conditions for which hormone therapy is a more or less specific therapy

1. The menopause

For the vasomotor symptoms of the menopause, gynecologists are agreed that estrogenic hormones are the therapy of choice. Many successful series have recently been reported (Albright,[29] Houghton and Neville,[30] Frank and Salmon,[27] Papanicolaou and Shorr[5]). A single recent study (Pratt and Thomas[31]) noted very little difference in the rate of improvement of cases treated by theelin and by other agents. The relatively small dosage employed by these workers is perhaps the explanation of their failure to get better results.

Theoretical estrin requirements in the complete absence of ovarian function have already been discussed. Review of various reports indicates, however, a vast difference in the recommended practical dosage in the menopause. Most workers seem to approve a plan of a relatively large initial dosage with a gradual reduction. The attempt should not be made permanently to maintain the patient at premenopausal levels of estrin blood concentration, but to make the usual abrupt onset of the menopause a gradual one. A convenient plan is to give by intramuscular injection

10,000 international units of estrone or estradiol benzoate twice a week for two or three weeks; then once a week for three weeks with at the same time about 500 to 1,000 units of estriol or some other preparation by mouth; then a period when the substance is given by mouth alone; with finally a period of gradual reduction of the oral preparation. The responsiveness of different patients varies greatly and a few may require as much as 50,000 units twice weekly at the start. Finally, it cannot be too strongly emphasized that a woman entering the menopause with few, if any symptoms, should not be subjected to any attempts at therapy.

2. Vaginitis

The demonstration of definite histologic alterations in the vaginal mucosa and changes in the pH of the vaginal secretions gives support to the belief that the estrogenic hormone is also a more or less specific agent for the treatment of certain vaginal conditions, notably gonorrheal vaginitis in children and atrophic vaginitis after the menopause. The reports on the treatments of these conditions are only a little less favorable than those for the menopause.

a. Infantile and juvenile gonorrheal vaginitis

The first report on the successful therapy of gonorrheal vaginitis in children was by Lewis[32] in 1933. Since then there have been many corroborative studies (Te Linde and Brawner,[33] Miller[34]). While some success may be obtained by hypodermic injections of 1,000 to 2,000 international units daily, Lewis and Adler[35] now recommend vaginal suppositories of 1,000 units each daily. They obtained 30 negative smears out of 33 cases treated on an average of 20.7 days. Although there seems little doubt of the real effectiveness of this treatment, relapses are prone to occur. It is at least possible that sulphanilamide will supersede the estrogens as the first therapeutic agent to be tried for this disease. No permanent ill effects are believed to result from the premature estrogenic stimulation of the reproductive tract, and although temporary hypertrophy of the breasts and uterus sometimes occurs, these changes disappear after the cessation of treatment.

b. Senile vaginitis and pruritus vulvae can be treated on a rationale similar to that for the cases of juvenile vaginitis. The proliferation of the epithelium and the disappearance of signs of inflammation after estrogen therapy has been begun have been demonstrated in a series of histologic sections from patients before, during, and after treatment (Davis[36]).

Many reports on this type of therapy have been favorable, both for vaginitis (Davis,[36] Jacoby and Rabbiner[37]) and for vulvitis with pruritus (Rust,[38] Klaften,[9] Wetterwald,[39] Schockaert,[40] Béclère[41]).

In the treatment of senile vaginitis care should of course be taken to exclude specific organisms, such as the Trichomonas vaginale, but after such causes have been excluded, estrogenic therapy appears to offer the best chance of success. As regards dosage, the widest possible range has been recommended. Davis[36] reported success with 100 rat units subcutaneously, three times a week, the average treatment lasting six weeks, and alleviation of symptoms being usually noted in ten days. Several writers recommend doses as high as 50,000 international unit equivalents of estradiol benzoate once or twice a week for periods of two months. Estrin in ointment (Klaften[9]) or a suppository has been given successfully. On the whole, it seems advisable to give a dosage similar to that employed for the vasomotor symptoms of the menopause, beginning with a dose of 10,000 international units twice a week and gradually reducing it, with a reservation of the dose of 50,000 units for the cases of failure with the smaller amount.

B. CONDITIONS FOR WHICH ENDOCRINE AGENTS MAY WITH JUSTIFICATION BE TRIED AFTER OR IN ASSOCIATION WITH OTHER THERAPEUTIC MEASURES

In this group of cases the value of endocrine agents is still a matter of dispute. Custom has somewhat justified their use. Nevertheless, success is not sufficiently consistent, nor is the rationale always clear enough to permit any of the hormones to be termed specific. No practitioner is justified in beginning and ending his therapy with their use, and heavy responsibility rests upon him if he fails to search for other than endocrine causes for the symptoms.

1. Amenorrhea

In approaching the therapy of amenorrhea in a younger woman, one must remember that the physiologic basis of the condition is quite different from that of the absent menstruation of the menopause. Complex disturbances in gland relationship, little understood, are present and the simple addition of the ovarian hormone is not necessarily the correct way to relieve the symptoms. Certain diagnostic procedures always must be carried out before sex hormone therapy can be con-

sidered. Constitutional disease, particularly tuberculosis, should be excluded and nutritional disturbances with marked abnormalities in weight attended to. Finally, the basal metabolism must be determined and, if abnormal, correct treatment instituted.

If therapy with one of the sex hormones is to be given a trial, a classification of the amenorrhea should be attempted. There are certainly several types: one, with absent or low ovarian function; one, much less common, with a high or normal ovarian function, the so-called polyhormonal amenorrhea (Zondek[24]). The differential diagnosis may perhaps be made by observing the condition of the pelvic mucous membranes; more definitely by endometrial biopsy or assay of the estrogenic or gonadotropic excretion in the urine. Many of these cases are probably instances of a primary pituitary disturbance, so that an anterior pituitary hormone is theoretically indicated. The luteinizing hormone of pregnancy urine is not, however, correct from a physiological standpoint, nor has it given satisfactory results. The follicle-stimulating hormone has perhaps not been given sufficient trial in adequate dosage to have its value known, but failures have been reported (Frank *et al*[42]).

There remains the estrogenic substance which in sufficiently large dosage will often produce some uterine bleeding. Its disadvantage is that usually the only period that occurs is that immediately following a course of therapy. This is to be expected since the drug is essentially substitutional. It is probable, however, that in some cases, 20 per cent according to Mazer and Israel,[7] the menstrual cycle is successfully "started up" after the first period, perhaps through some effect of the massive dosage on the pituitary. An occasional conception has also been reported following such therapy.

The dosage required to produce a menstrual period in an amenorrheic woman is more variable than in a surgical castrate or a woman in the menopause. Rock used an average of 50,000 rat units of "folliculin" and 50 rabbit units of corporin over a three-week period. Mazer and Israel,[7] although reporting a high percentage of temporary successes, had one failure in a patient receiving a total of 675,000 rat units. Frank and his associates,[42] using doses from 80,000 to 3,450,000 international units noted no responses below 1,000,000 international units, and a failure was recorded with the highest dose given. It appears clear, as these workers point out, that other factors besides ovarian deficiency are responsible for amenorrhea.

Amenorrhea in itself is probably not harmful and only in an occasional case will it appear justifiable to give injections of estrogenic hormone. When this agent is employed, short courses with relatively high dosage, possibly 50,000 international units every other day for two weeks, should be given with intervals of a week or two of rest in between. Corpus luteum hormone given in doses of one to five units every day for three or four days at the end of the course of estrogenic therapy may serve to make the bleeding, if it occurs, histologically more realistic, but it is questionable whether it contributes anything toward a permanent cure (Elden,[43] Rock[44]). Such treatments, as outlined, are very expensive and the chance of lasting improvement is small.

In most exceptional cases, presumably in those of polyhormonal amenorrhea with cystic ovaries, two other methods of approach may be of help. One is the use of so-called stimulating x-ray to the ovaries, for which considerable success has been reported (Kaplan[45]). The other is a surgical operation with removal of a part of each cystic ovary (Robinson[46]).

2. *Abnormal Uterine Bleeding*

A careful exclusion or correction of organic causes of uterine bleeding is essential before any endocrine therapy is to be thought of. Systematic physical examination will disclose the majority of these organic lesions, but the possibilities of an endometrial polyp, submucous fibroid or retained placental fragment, even of endometrial carcinoma, will remain. Before the age of forty the frequency of the last cause is so small as to justify some delay in the performance of a diagnostic curettage, but in older patients the physician accepts considerable responsibility in attempting a hormone therapy without first exploring the uterine cavity.

The plan of treatment adopted for abnormal uterine bleeding will therefore differ markedly according to the patient's age. Before the fortieth year endocrine therapy—thyroid extract in cases with a low basal metabolism or either the luteinizing or the corpus luteum hormone itself—may justifiably be tried. After the age of forty, if bleeding recurs following curettage, the best plan is probably to resort at once to some form of radiation therapy with the aim of suppressing completely the ovarian function. Whether, following curettage, hormone therapy is of value to prevent return of the bleeding, is at present unknown and will

be difficult to prove.

The use of the luteinizing hormone of pregnancy urine has already had a number of years of trial. Novak and Hurd[11] in 1931 reported improvement in all but seven of fifty-one cases and recommended a dose of 200 rat units, to be repeated one to six times. Wilson and Kurzrok[47] stated in 1936 that practically every case of functional uterine bleeding could be controlled with pregnancy urine extract if adequate dosage were employed. Their recommended average dose during periods of active bleeding was 200 to 750 rat units daily, followed when the bleeding ceased by 200 rat units once or twice a week for several weeks or months. In contrast to the optimism of these reports is a growing scepticism among many gynecologists, as well as a few definite reports (Keene and Payne[48], Jeffcoate[49]) which indicate that the brilliant claims of the early investigators are not being substantiated. Opinion is crystallizing that this hormone justifies a trial in bleeding during early and middle life, but that failure frequently follows its use even in these years, and other methods must often be resorted to (Meigs,[50] Smith and Rock[51]).

Corpus luteum hormone has also been advocated for menorrhagia and metrorrhagia (Wilson and Elden,[52] Stemmer,[53] Preissecker[54]) with the object of luteinizing the endometrium which in certain forms of functional bleeding is characterized by a morphology believed to be estrogen-produced. Although Wilson and Elden[52] have written of successes with small fractions of a rabbit unit, such dosages seem inconsistent with the amounts needed to produce a progestational change in the castrate uterus. Few clinical reports are available, but it would appear that if this form of therapy is to be tried, a dose of at least one rabbit unit daily should be given for several days before the expected excessive period is due, or during intervals of abnormal bleeding.

3. Dysmenorrhea

The theories offered to explain the so-called primary or essential dysmenorrhea are sufficiently varied to furnish grounds for almost any type of endocrine therapy. If the disease is due to the myometrial insufficiency of an underdeveloped uterus, one may with reason recommend an estrogenic substance, while if it is due to a hypersensitivity of the musculature from excessive estrin, then a corpus luteum hormone is to be advised. On the other hand, adherents of a mechanical theory still exist who feel that a dilatation of the cervix or a straightening of the

canal by a stem pessary is the only direct approach to the problem. With the cause of the symptom still unknown, some empirical but systematic plan must be adopted which will start with the simplest measures and work up slowly through the more complicated, in the hope that a means to give relief may be found without the necessity of resort to surgery.

It is again essential that secondary dysmenorrhea due to organic lesions be carefully excluded before the endocrines are thought of. When the pain appears only after several years of normal periods, one must search especially for such conditions as inflammatory disease, a myoma or adenomyoma, or a congested pelvis with uterine malposition.

If no organic basis is found, the next step is to review the possibilities of excessive fatigue, nervous stress, constipation, and other factors capable of affecting the autonomic nerves and the vascular system of the pelvis. An adjustment of the patient's daily activities and the improvement of her general health will yield the largest fraction of the cures to be obtained by the entire list of therapeutic procedures.

If general measures fail, endocrine therapy may be tried, because it is simpler than any form of surgical approach. Two hormones may be considered, estrogenic for the hypoplastic uterus, and corpus luteum for the hypercontractile one (Cannon[55]). Both conditions are admittedly somewhat theoretical entities, especially the latter. In general the patient with a uterus of normal size is most logically treated by progesterone, and with this therapy some successes have been noted (Elden and Wilson;[56] Lackner, Krohn and Soskin;[57] Kotz and Parker[58]). Although smaller doses have been reported as effective, a rabbit unit given every other day during the fourteen days preceding menstruation would appear to be a minimum reasonable dosage. Instead of the corpus luteum itself, the luteinizing factor from pregnancy urine has been advised (Novak and Reynolds,[59] Browne[60]). On the other hand, in patients with very small uteri, estrogenic substance usually administered during the first half of the cycle may be given, either alone or preceding the progesterone injections of the latter half of the month.

It must finally be re-emphasized that no one has yet proved that dysmenorrhea is an endocrine disease, to say nothing of demonstrating the type of glandular dysfunction present. Endocrine therapy of the present types may be counted upon to give frequent failures. The passage of time, marriage and conception are still the factors which determine

the final cure for most women. On account of the occasional necessity for immediate relief, there is still a place for dilatation of the cervix, rarely the suspension of a retroverted uterus, exceptionally perhaps the resection of a presacral nerve.

4. Sterility

An imposing list of diagnostic procedures must be carried out in cases of sterility before a position is reached where hormone therapy is permissible. The male must be examined and the semen studied. Gross lesions in the female pelvis must be excluded, the patency of the tubes determined and any minor infection of the cervix cleared up. The diet should be considered and gross nutritional defects corrected. In the majority of cases a cause for the sterility will be found during these procedures.

If the endocrine field is to be explored, the determination of the basal metabolism is undoubtedly the first step. Cases of hypothyroidism treated with thyroid extract are generally agreed to give the most favorable results in this difficult group. Beyond this is uncertain ground. If the uterus is underdeveloped, relatively small doses of estrogenic substance may be given during the first half of the menstrual cycle over several months time. Kurzrok's[12] recommendation of not more than 75,000 to 100,000 international units, parenterally, or five times that amount by mouth during any one cycle, seems a logical one. In a certain proportion of cases endometrial biopsies, taken shortly before menstruation, may give an indication of the degree of corpus luteum activity and perhaps show the absence of ovulation. In these cases corpus luteum hormone or a follicle-stimulating hormone to induce ovulation may be tried. Finally, when other methods have failed, success may sometimes be obtained by "stimulating" doses of x-ray to the ovaries (Rubin,[61] Kaplan[45]). Even resection of the enlarged cystic ovaries has been recommended, but is not now often resorted to. Surgical procedures should only be undertaken when the patient's desire or need of a child is very great, and she should not be deceived as to the probable chances of success.

5. Habitual and threatened abortion

The causes of abortion are far from understood and it is probable that many are rooted in primary defects of the ova or spermatozoa.

Nevertheless it is tempting to believe that a corpus luteum deficiency, acting either to cause a defective decidua or an overactive myometrium, may play a part in abortion. Providing that other causes are carefully considered, such as hypothyroidism, dietary deficiencies, and organic disease in the pelvis, it is permissible to add corpus luteum as a part of a plan of treatment. Numerous clinical reports are available to indicate its value. Falls, Lackner and Krohn[62] in 1936 reported success in all but seven of forty-one cases of so-called habitual and threatened abortion. They recommended one rabbit unit twice a day in cases of threatened abortion until the symptoms had subsided and in cases of habitual abortion one rabbit unit prophylactically twice each week until the thirty-second week of pregnancy. That Kane[63] in the same year obtained equally good results from treatments with only 1/25 of a unit is another example of the uncertainty of dosage with these substances. Furthermore if, as appears probable, the smaller dosage was physiologically insignificant, the series of Kane may serve as a control to show what is to be expected in cases of repeated abortion when they are given simply the best of general attention without specific treatment.

6. Chronic cystic mastitis

For a number of years certain diseases of the breast, notably that associated with a painful nodularity, have been treated with estrogenic substances. The reported results have been equally good whether the therapy has been by the undoubtedly inert tablets of ovarian residue of 1931 (Cutler[64]) or the potent preparations of 1937 (Lewis and Geschickter[15]). Indeed, with the current belief in the estrogenic *cause* of many breast lesions, to find a rationale for an estrogenic *therapy* requires a dextrous rearranging of the physiologic diagrams of endocrine interrelationships.

The above is a personal opinion and it must at once be conceded that many clinical reports do indicate a favorable effect when estrogenic hormone is given to cases of chronic mastitis. In cases in which the possibility of a malignant neoplasm has been unquestionably excluded and the symptoms are severe enough to merit any therapy, estrogenic hormone may be tried. The plan of therapy advocated by Lewis and Geschickter[15] is to give 10,000 international units at each injection, twice a week for six doses the first month; once a week for three doses the next month; twice the third month; and once during the premenstrual

weeks of the fourth, fifth and sixth months of therapy.

In a rare case of marked painful congestion of the breasts in patients near the menopause, radiation of the ovaries will offer a successful means of endocrine therapy. The dramatic relief which follows a reduction in the ovarian function more than compensates for a slightly premature menopause in exceptional cases of this type.

IV. Conditions for which Endocrine Agents are on too Untried a Basis for General Use

There is, finally, a long list of conditions for which the sex hormones have occasionally been tried, but for which the conscientious physician should resort to endocrine therapy with considerable hesitation. The conditions placed in this group have been so classed for several reasons. First, the indications may be relatively rare and sufficient cases have not yet accumulated to afford material for adequate trial. Second, the original reports of success may have remained relatively uncorroborated and the silence of other physicians be suggestive of disappointment. Finally, the general nature of the condition, as we now know it, may be such as to make the sex hormones appear too remotely related to promise an effective influence. It is conceded that arguments could easily be brought to transfer certain of the conditions listed in group III to group II and vice versa. Certainly it is probable that the next few years will see many changes in classification. In general, however, a case may be made for the statement that the endocrine treatment of the diseases to be listed in group III has neither the support of proved efficiency, of established rationale, or even of accepted practice.

The conditions which might be placed under group III are too numerous for more than an incomplete list.

A. estrogenic hormone

1. Hypertension (Schaefer;[68] Wallis;[66] Fellner[67]). 2. Involutional melancholia (Schube and associates,[65] Sevringhaus,[69] Werner[70]). 3. Migraine (Glass;[71] Blakie and Hossack;[72] Thomson[73]). 4. Frigidity. 5. Epilepsy (Schaefer and Brosius[74]). 6. Eclampsia (Shute[75]). 7. Vomiting of pregnancy (Hawkinson[76]). 8. Postmaturity and missed abortion. 9. Uterine inertia (Robinson[77]). 10. Menopausal arthritis. 11. Urinary incontinence (Hoffmann[78]). 12. To delay menstruation (Foss[79]). 13. Hemophilia (White,[80] Kimm and Van Allen,[81] Birch[82]). 14. Atrophic

rhinitis (Mortimer, Wright and Collip[83]). 15. The Cushing syndrome (Dunn[84]).

B. GONADOTROPIC HORMONE

1. Migraine (Moffat[85]). 2. Acne vulgaris (Lawrence[86]).

C. PROLACTIN

1. Deficient lactation (Kurzrok, Bates, Riddle and Miller[14]).

D. CORPUS LUTEUM HORMONE

1. After pains (Lubin and Clarke[87]). 2. Pernicious vomiting. 3. Premature labor.

Conclusion

The present status of gynecologic endocrine therapy places the physician in a dilemma. He cannot forswear these substances completely, because his patients will demand them. He cannot use them too frequently without appearing something of a charlatan to his more sceptical colleagues.

A year or so ago an editorial in the *Journal of the American Medical Association* (October 24, 1936) urged that only those physicians with facilities for critical study be encouraged to administer the new preparations and that other physicians should "cease their indiscriminate injections of unknown substances into unsuspecting patients." This advice cannot and should not be taken too literally. The physician with facilities for critical study has produced too many studies far from critical. Furthermore, a report of a percentage of successes with a new plan of therapy from a large clinic is only the beginning of its trial.

A new endocrine preparation, after one or two series of cases have been published, must be subjected to the test of its use in practice. Its final adoption will depend not upon whether a certain per cent of a series of fifty women are benefited, but whether it is sufficiently dependable to be used on a special case in whom an individual practitioner is individually interested. That the final test rests, therefore, with the general profession gives justification for the present cautious administration of these substances.

The use of the so-called sex hormones, however, involves certain

responsibilities. He who prescribes them must be certain of at least three things: (1) that conditions other than an endocrine disturbance have been excluded as the cause of the symptoms; (2) that experienced authorities regard the new material as safe; (3) that there is a rational basis and at least some expert testimony to the efficacy of the substance in treating the disease for which it is to be given.

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THE PATHOLOGICAL RESPONSES TO VITAMIN DEFICIENCIES*

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THE great reward of our efforts to understand the accessory food factors lies in improved nutrition. It is generally believed that we already see signs of this in an improved physical constitution of the younger generation, and a falling morbidity rate of diseases for which no specific control measures have been taken. Naturally this is of great interest to physicians. But there is another side to the subject which is of still greater interest, the morbid consequences of vitamin deficiency. While of distinctly less importance, this phase of the problem is so closely related to the problems with which physicians must constantly cope that it has attracted a great deal of attention.

Physicians have indeed become so actively interested in the vitamins that last year more than one thousand reports were published on the subject—ten times as many as were devoted to the virus diseases. The activity has become so intense that considerable confusion has necessarily followed. In such a situation it seems proper to consider representative vitamin deficiencies from the anatomical point of view, not only to demonstrate that thoroughly dependable anatomical criteria exist for several of these conditions, but also to show how the morphological evidence may be used further to advance our understanding of the subject.

A great deal has been known about the pathological anatomy of the deficiency diseases for a rather long time. The older pathologists had ample opportunity to study all of these diseases and to observe the lesions. Rickets was well understood long before vitamins were discovered and scurvy was not only accurately described but very keen inferences drawn concerning its nature and pathogenesis. Certain lesions were observed and largely forgotten. Thus, colitis cystica superficialis was rediscovered by Denton[1] as characteristic of acute pellagra many years after its original recognition.

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The earlier pathologists contended with two handicaps. In the first place, the deficiencies were usually multiple. This greatly complicated the lesions and led to marked difficulty in distinguishing between rickets and infantile scurvy. In the second place, most of their cases died of other, more dangerous complications, usually infectious diseases. Deficiency disease is relatively seldom the immediate cause of death, an observation which turns out to be of considerable importance to students of infectious diseases as well as nutritionists.

The great gift the biological chemists contributed was the opportunity for the study of controlled, graded cases of individual deficiencies and the exclusion of complicating diseases. Once this was achieved, the anatomical studies progressed rather rapidly, so that today it is possible to ascribe fundamental, specific effects on certain specialized tissues to each of several vitamins.

Vitamin A deficiency is an example. Some years ago the nutritionists spoke of this vitamin as a growth-promoting and anti-infectious food factor. This designation was based on the observation that when a young animal was deprived of vitamin A, growth ceased and the eyelids became matted together with exudate, while abscesses developed under the jaw. By the application of pathological criteria, it was discovered that the evidence of infection was only secondary to a remarkable metamorphosis or metaplasia of the epithelium of the ducts of the salivary glands and elsewhere. The normal columnar cells were observed to become replaced by stratified, squamous epithelium which rapidly became keratinized.

A keratinized cell is very durable and when found within the body is treated as a foreign substance. It is resistant to proteolytic enzymes and when such cells accumulate in a duct they obstruct the flow of secretions. Since an obstructed gland usually becomes an infected one, the anti-infectious nature of vitamin A was seen to be only an accidental, secondary effect of a much more significant morbid process. The eye lesions were due to a similar metaplasia of both the tear glands and the cornea. Other epithelial surfaces, including the urogenital tract and the respiratory passages, were found which behaved similarly. In man, the follicles of the skin become so filled with keratinized epithelium that they create the appearance of a toad's skin.

This is the essential lesion of vitamin A deficiency. It is a very sensitive criterion. A careful observer may establish its presence in the female

rat very early in deficiency by noting the prolongation of the stages of estrus characterized by keratinized vaginal cells. It is a yardstick by which we can determine a morbid consequence of vitamin A inadequacy in a given animal: but is it a *specific* effect?

Epithelial metaplasia was not a new lesion to pathologists. It had frequently been seen in various tissues. Its cause was, however, a complete mystery. Severe, generalized forms occurred in cases of prolonged, obstructive jaundice. In the days of intubation for croup it had at times been observed in the trachea where the cannula pressed against the mucosa, but efforts to produce it experimentally by cannulae only seldom succeeded. It was seen most often near foci of chronic inflammation and recently the endocrinologists had discovered that massive doses of theelin produced metaplasia in the endometrium of rodents.

We have tested the specificity of epithelial metaplasia in two ways. Whenever we discover a patch of metaplastic epithelium in tissues removed surgically, we search the patient for clinical evidence of vitamin A deficiency. This has not often been successful, possibly because of the delay between inauguration of hospital diet and our examination of the surgical specimen—a period long enough to allow of repair.

We have also tested experimentally the relative influence of vitamin deficiency, theelin and irritation.[2] The results of these trials have been most interesting. Irritation, as from a thread tied through the trachea, will produce metaplasia if the vitamin A intake is low, and will hasten the appearance of metaplasia if the deficiency be profound. But if the vitamin intake be large, neither mechanical irritation nor theelin dosing produces metaplasia. Indeed, an advanced stage of metaplasia produced by theelin will promptly undergo repair if ample vitamin be given. It therefore seems that vitamin A is the critical factor in experimental epithelial metaplasia.

However, these experiments go further. We have learned that more vitamin is needed to prevent metaplasia in rats given theelin than is required by normal animals and also that in the theelin-treated rats, the lesion of vitamin A deficiency occurs only in the uterus. In other words, theelin does not produce a systemic deficiency disease but only a local one, presumably by so exaggerating the rate of growth of the endometrial epithelium that the local requirements of vitamin are correspondingly exaggerated. The irritation experiments led to the same conclusion. Thus, the experiments seem to demonstrate a local morbid process, due

to a local deficiency in an animal receiving a maintenance dose of vitamin A. Such a conception extends the field of the pathology of the avitaminoses still further.

For example, it has been shown recently that many patients with renal calculus have stigmata of vitamin A deficiency (night blindness) and that most of these remain in this condition despite the prolonged administration of doses of vitamin A as great as 50,000 International Units daily.[3] It has been suggested that this is because they either do not absorb vitamin properly or fail to utilize it normally. It seems to me that we might consider that such persons have an *irreversible* form of vitamin A deficiency.

These new conceptions of the rôle of vitamin A, the local deficiency lesion and the irreversible one, might then be added to the list of deficiency effects due to faulty absorption, abnormal excretion by the kidneys, excessive destruction in the stomach or bowel, deficiency consequent to liver disease, the abnormally high requirement that alcoholics seem to have for vitamin B_1, which is also present during pregnancy and infancy. It becomes evident that the known clinical forms of the deficiency diseases are the lesser part of our problem.

Vitamin C is likewise essential to the maintenance of a particular tissue—in this case the skeletal structures. The primary morphological effect of scurvy is seen in the bones, teeth, muscles and fibrous tissue. These are formed largely of intercellular materials which, in the absence of vitamin C, are of a different physical nature. They remain fluid, the form in which they are secreted. If vitamin be administered they rapidly solidify.

As far as may be judged by observation alone, this resembles the setting of a gel. It appears abruptly at some distance from the cell membrane, suggesting that the intercellular materials and not the cells are primarily affected. This theory is supported by the rôle the vitamin is known to play in oxidation-reduction phenomena in the tissues and the importance of hydrogen ion concentration to colloidal systems.

It is rather surprising how sensitive the anatomical criteria of scurvy are. A little practice and attention will disclose clues to this disease in much human material. Edwards Park's experience is instructive in this respect.[4] Two years ago, he and his colleagues analyzed 125 cases of scurvy. About one-sixth of these were found among 500 postmortem examinations which Dr. Martha Elliott, under the auspices of the United

States Children's Bureau, had started to collect at the New Haven Hospital. The work was later transferred to the Harriet Lane Home in Baltimore. The original purpose of the study was to determine the nature and extent of rickets by anatomic and radiographic examinations. Rickets was present in 27 per cent of this group; scurvy in 4 per cent. Of the nineteen cases having distinct anatomical evidence of scurvy, only two had been diagnosed before death and only seven by the pathologists who first studied the cases.

This is probably a rather representative record. It is worth noting two reasons which Park gives for the failures. In the first place, most of the children were suffering from another, more dramatic disease which absorbed the full attention of the physicians; and in the second place, the habit had been to look for scurvy among the children who were feeding problems; not, quite illogically as it turned out to be, among those having pneumonia and meningitis.

This interesting observation supports the recent demonstration that the vitamin C requirements of individuals sick from severe infectious diseases are abnormally high. Is there any morphological evidence to support this? There is the experience of Park, of course, and there is another possibility which might be considered with this in mind.

One of the lesions of scurvy is degeneration and fragmentation of the skeletal muscles. This was very conspicuous in years long past when severe scurvy was common. The muscles turned to "currant jelly" and were sometimes so extensively diseased that the patient became paralyzed. The lesion in these cases seems to be identical with what we have designated as Zenker's degeneration. It has a rather interesting history. Zenker was not the first to observe it but was the first to show its frequency, especially in typhoid fever. There it was so regularly present that it became an important postmortem clue to the disease.

Its most recent frequent occurrence was during the great influenza epidemic. Wolbach and Frothingham and MacCallum observed it in influenza deaths. Since, there have been but few and meager reports and while during the World War Beneke was able to find it in all infants dying of sepsis, it seems now to have become relatively uncommon or even rare.

The same lesion may be produced experimentally by vitamin C deficiency, by trauma, the injection of caustics and by a diet devised by Goettsch and Pappenheimer which is not deficient in the known vita-

mins. But in man its occurrence seems to be largely limited to severe infectious diseases and to scurvy.

The question seems unavoidable whether the infectious diseases with their high vitamin requirements and the older practice of feeding gruel and broth did not actually precipitate Zenker's degeneration by precipitating scurvy. So far the evidence is circumstantial. One is reminded of Coleman's demonstration twenty years ago of a negative nitrogen balance during typhoid fever, quite comparable to the negative vitamin balance found today. Beneke's experience is wholly harmonious, for the evident widespread occurrence of Zenker's degeneration in Germany during the War agrees with what we know of the incidence of mild scurvy during that time.

Perhaps these several illustrations will amply indicate the engrossing fields of pathological study which the vitamins have opened to us and demonstrate how these factors may play a large part in conditions apparently quite removed from the deficiency diseases as we know them. To me it seems to show likewise the necessity of a critical consideration of the diets used in most biological experiments, for the constitution of the diet modifies biological phenomena in many ways.

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OUR VITAMIN B_1 SUPPLY IN RELATION TO HUMAN NEEDS*

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THE vitamins must be viewed by the medical practitioner from a rather unique standpoint. They are not drugs and exhibit little pharmacological action in normal animals. They perhaps resemble hormones in respect to their high quantitative potency but differ from hormones sharply in that they are derived from external rather than internal sources. As components of foodstuffs, they have an apparent relationship to other components of food. One might plausibly think of some of them as related to the specific amino acids which have been found essential to proper nutrition. However, the vitamins differ from these components of food, according to the best existing evidence, in that they appear to be parts of necessary mechanisms rather than necessary building stones for the tissues.

Our topic this evening has to do with the choice and use of human food which is necessary to assure the maximum health and longevity. However, the mode of action of the vitamins is so fundamental to any sound philosophy in the matter that we must digress a moment to review the developments of the past two or three years concerning the physiological rôle of this category of substances. It has been shown that thiamin (vitamin B_1) in the form of its pyrophosphate is a coenzyme; that is, a component part of enzyme systems having to do with carbohydrate metabolism. More particularly it has to do with the metabolism of pyruvic acid, a necessary intermediate in carbohydrate utilization. Carbohydrate metabolism is almost certainly a necessary function of nearly all living cells. The evidence is that thiamin pyrophosphate takes part in this metabolism of cells, whether they be those of bacteria, molds, fungi, higher plants, insects, or higher animals. The pathway whereby carbohydrate is metabolized appears to have much in common regardless of the type of cell with which one is concerned. Aside from the special function which each organ of a higher animal performs for the benefit

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of the body as a whole, there are processes of derivation of energy from carbohydrate which are carried on alike in each cell of all tissues. These are necessary for its own survival and vital activity. Thiamin, therefore, appears to be a fundamentally essential tool of metabolism, necessary for all living things.

What appears to be true for thiamin in high degree appears also to be true to a considerable degree for the other water soluble vitamins. Thiamin is merely the most conspicuous example, because nature's total supply is not much in excess of minimum needs and because the lack of no other accessory substance leads to so prompt, so profound and so universal a disaster.

It is consistent with this view that all plant and animal tissues contain this substance. However, the capacity for synthesis of the substance in nature is sufficiently limited so that no natural tissue is by accident super-rich in it. Whereas the majority of plant and animal tissues which are used as foods contain about one-half part per million of it, the richer foods contain only three to five parts per million. Notable among these are the seeds which constitute a principal repository of the substance in the plant world. The germs and bran coats of grains may contain thirty to fifty parts per million, these larger amounts being stored in the seed to care for the growth of the plant until it puts forth leaves to the sun and can then resume synthesis of the vitamin. Many of the lower plants have very meager capacity for its synthesis; some lack it entirely; none produce a plethora of it. The richness of brewers' yeast in vitamin content is primarily due to seizure of it from the grain wort in which the yeast is grown. If nature as a whole operates on an economy of scarcity with respect to this substance, it is not surprising that mankind should appear to do so also.

The foods may be divided into three groups:

A. Thiamin-rich foods, notably seeds, lean pork, and to a lesser extent milk and the internal organs of mammals.

B. Thiamin-poor foods, such as highly milled grains, hominy, macaroni, polished rice, white bread, sugar.

C. Indifferent foods which comprise everything else except fats. These foods, such as fruits and vegetables, contain significant amounts of thiamin per unit of dry weight but do not provide a sufficient surplus to make up for the deficiencies of the thiamin-poor foods, unless the latter are used in relatively small quantities.

D. The Fats. These do not require thiamin for their metabolism and in so far as they serve to displace foods of class B from the dietary, they have a very valuable protective effect.

We recently have had occasion to reanalyze seventy diets associated with historical outbreaks of beriberi and about thirty diets associated with absence or recession of the disease. The diets in question are among those previously analyzed by Cowgill. After trying various indices, we found that the ratio between the thiamin content of the food and its non-fat calorie content is an excellent index of the appearance or non-appearance of beriberi. If the thiamin is stated in micrograms (millionths of a gram) and the calorific content in small calories, we get a relationship $\frac{\text{thiamin}}{\text{non-fat calories}} = .3$ as representing the borderline between beriberi and non-beriberi.

This index also fits quite well the diets of the working classes in the United States, to judge from a considerable number of them to which it has been experimentally applied. The contrast between the Oriental beriberi-producing diets and poor class American diets is not great with respect to thiamin content. The latter diets owe such superiority as they possess as much to the presence of larger amounts of fat as they do to the presence of larger amounts of thiamin. American diets in which white bread, corn meal and like products make up a large part of the calories are near the beriberi borderline. The diets of more prosperous people show a considerably larger margin of safety due principally to the lesser proportions of starchy foods. It should be said, however, that many of the Oriental diets used by peoples who are not addicted to the milling of grain often contain as much or more thiamin than the average American diet.

An attempt has been made by Cowgill to relate the thiamin requirement to the individual weight. He concluded on the basis of animal experiments that the thiamin requirement of an individual is proportional to weight$^{5/3}$; that is, that in a series of individuals the requirement rises much more rapidly than the weight. The experiments in question were performed before it was well recognized that there is a large number of B vitamins. In the light of recent knowledge, the basal diets which were used were deficient with respect to several of these factors. We believe that the apparent rising proportional require-

ment with rising weight is due to the fact that larger doses of crude vitamin were necessary, not to supply sufficient thiamin, but to supply sufficient, or more nearly sufficient, amounts of the other B factors which were also present in the crude product, but in lesser proportions.

Cowgill recognized that the requirement per unit of body weight is much larger for small species of animals than for large species, an idea which has general support. Combining these two theses, he gives us a picture of animal needs *rising* with individual weight within a species but *falling* as individual weight rises from species to species. This does not seem reasonable for it implies that species divisions represent sharp breaks in respect to metabolic economy in the animal world, whereas we have long been accustomed to think of the various species as physiologically akin, differing from one another by small gradations.

If one abandons the idea of the vitamin requirement rising in proportion to weight$^{5/3}$, as one is justified in doing on the basis of recently gained knowledge with regard to the multiplicity of B vitamins, one arrives at a much more reasonable and consistent picture. It is, that the required proportion of thiamin to non-fat calories of the food is substantially constant for all species and all weights. The quantity of food which is required, and therefore the *quantity of thiamin* per unit of body weight, rises in a general way as the weight falls whether within a species or from species to species, approximately in proportion to weight$^{2/3}$. This is a reflection of the fact that the body surface and the consequent heat loss from the surface rises as size decreases. The increase of food requirement (calories) with diminishing size is, of course, not a precise proportionality as it is affected by many factors, such as activity, habitat, or furry covering. In a rough way, however, it is true for warm blooded animals.

As far as the *proportion of thiamin* in the food is concerned, the requirement of all warm blooded animals is substantially the same, as far as our present knowledge permits us to judge. (An adjustment for proportion of fat in the customary food would be necessary.) One is tempted to surmise that the animal world gets as much thiamin as the plant world is able to supply and that this amount affords little margin above the requirements for health and well-being of all the creatures which evolution has produced. In favor of such a view is the fact that enrichments of supposedly normal diets have often been observed to result in superior performance. Some plants which can synthesize thiamin

also respond favorably to a supplemental external supply.

Animals are not economical of thiamin but tend to waste any excess above their needs. An increase in the intake is promptly reflected in an increase in the excretion in the urine. Storage in the body against a later time of need is quite limited. In quantitative terms, the human requirement for the prevention of beriberi is about one milligram for each 3700 non-fat calories of food intake. For diets containing large proportions of starch and small proportions of fat, such as prevail for a great part of the working population of the world, the minimum daily requirement per adult is apparently not far from 0.6 milligrams or roughly 200 International Units per day for a 2500 calorie intake.

We have previously emphasized the bran coats and germs of seeds as the principal repository of thiamin in foodstuffs of plant origin. As Robbins and others have shown, excised tomato roots are able to grow in artificial nutrient media in proportion to the thiamin added, over a wide range of values. It seems clear that thiamin is present in the seed to enable the plant to metabolize the starch placed there for its nourishment during its early weeks of growth. If plants, which can synthesize thiamin, are compelled at certain stages to fall back upon reserve stores of thiamin in order to utilize starch, it seems utter folly for mankind to consume the starch and carefully to discard the mechanism provided by nature for its metabolism.

The foregoing view of nature's economy of thiamin (and to some extent all other water soluble vitamins) rationalizes vitamin therapy much more satisfactorily than has heretofore been possible. It is no longer mere superstition that an abundant supply of thiamin may have therapeutic value in conditions which are not necessarily associated with any *sub-average* intake of thiamin in the food supply of the patients. The intake may be merely *sub-optimal*. If thiamin constitutes a necessary mechanism of metabolism for all cells, it is readily conceivable that an increase in the supply of this essential substance may result in an improved functional performance of whatever organ may be operating at low efficiency. Thiamin is not peculiarly a nerve vitamin; nerve tissue is merely peculiarly susceptible to the effects of a metabolic disturbance which simultaneously affects adversely but less conspicuously the functioning of all other organs.

In closing I want to extend my sympathy to the medical practitioner who must endeavor to keep track of a host of new therapeutic agents,

many of which bear purely arbitrary names, such as vitamin A, B, C. To add to his troubles, their potencies are often expressed in arbitrary units which are related, not to the performance of human beings, but to the daily needs of some small experimental animal. In addition, two or three different sets of units are often used. It may be a memory aid for such practitioners to remark that, whatever system of units is used for the vitamins, it requires several hundred units of any of the vitamins to afford a significant dose for a human adult. In the case of vitamin A, several thousand units are needed.

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DEATHS OF FELLOWS

CORYLLOS, POL N., 894 Madison Avenue, New York City; born in Patras, Greece, November 2, 1879; died in New York City, July 26, 1938; graduated in medicine from the University of Athens in 1901; elected a Fellow of the Academy March 7, 1929.

Dr. Coryllos was a member of the State and County Medical Societies, a Fellow of the American Medical Association and the American College of Surgeons, a member of the American Society of Thoracic Surgeons and the New York Society of Thoracic Surgeons. He was Director of Thoracic Surgery at the Metropolitan, Sea View and U. S. Veteran's (Castle Point) Hospitals, Associate Surgeon and Director of Thoracic Surgery at Polyclinic Hospital, Consulting Thoracic Surgeon to Broad Street and Staten Island Hospitals, Consulting Surgeon to St. Luke's Hospital at Newburgh, and Thoracic Surgeon to the Out-Patient Department of the New York Hospital.

FRANKLIN, MELVIN M.: 1911 Spruce Street, Philadelphia, Pennsylvania; born in Philadelphia, Pennsylvania, August 13, 1874; died in Point Pleasant, New Jersey, July 31, 1938; graduated in medicine from the University of Pennsylvania in 1895; elected a Fellow of the Academy January 6, 1910.

Dr. Franklin was visiting orthopedic surgeon to the St. Joseph's Hospital and consulting surgeon to the St. Joseph's, Mercy and Jewish Hospitals of Philadelphia and the Bamberger Memorial Hospital of Atlantic City, New Jersey.

He was a Fellow of the American Medical Association and the American College of Surgeons and a member of the County and State Medical Societies.

MOONEY, HENRY WALTON: 1 West 85 Street, New York City; born in New York City, July 19, 1861; died in New York City, July 17, 1938; graduated in medicine from the University of New York in 1891; elected a Fellow of the Academy October 6, 1904.

Dr. Mooney was a member of the State and County Medical Societies.

STEWART, JOHN DILLON: 580 Park Avenue, New York City; born in Newark, Ohio, November 22, 1880; died in New York City, August 3, 1938; graduated in medicine from the Medical College of Indiana in 1905; elected a Fellow of the Academy February 7, 1938.

Dr. Stewart was attending surgeon to the Post-Graduate Hospital and professor of clinical surgery at the Graduate School, Columbia University, College of Physicians and Surgeons.

He was a Fellow of the American College of Surgeons and the American Medical Association, and a member of the American Proctologic Society and the County and State Medical Societies.

WIENER, JOSEPH: 30 East 40 Street, New York City; born in New York City, March 24, 1872; died in Lawrence, Long Island, New York, August 28, 1938; received the degree of Bachelor of Arts from the College of the City of New York in 1890 and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1893; elected a Fellow of the Academy February 1, 1900.

Dr. Wiener was associate attending surgeon to the Mount Sinai Hospital for many years. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association and a member of the New York Surgical Society and the County and State Medical Societies.